Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee

Gadolinium-Based Contrast Agents & Nephrogenic Systemic Fibrosis
FDA Briefing Document

Advisory Committee
December 8, 2009

Content of this Briefing Document:

Clinical Review

Chemistry Review

Office of Surveillance and Epidemiology (OSE) and Office of Translational Sciences (OTS) Review

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List of Abbreviations

Abbreviation	Full Term
CHMP	Committee for Medicinal Products for Human Use, EMEA
CKD	Chronic Kidney Disease
EMEA	European Medicine Agency
FDAAA	Food and Drug Administration Amendment Act of 2007
GBCA	Gadolinium-Based Contrast Agent
GFR	Glomerular Filtration Rate
PhVWP	Pharmacovigilance Working Party
MAH	Market Authorization Holder
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography
NFD	Nephrogenic Fibrosing Dermopathy
NSF	Nephrogenic Systemic Fibrosis
OSE	Office of Surveillance and Epidemiology, FDA
PHA	Public Health Announcement
PMR	Postmarketing Requirement
SAG	Scientific Advisory Group

Executive Summary

This advisory committee is convened to review data pertaining to the development of nephrogenic systemic fibrosis (NSF) in association with gadolinium-based contrast agents (GBCAs). Specifically, FDA seeks the committee's advice regarding measures to minimize this risk. FDA is particularly interested in differential risk considerations among the agents (e.g., uniquely higher or lower risks with certain agents) and other considerations that should be addressed in labeling or other risk-reduction methods.

GBCAs are contrast agents used in magnetic resonance imaging (MRI) to improve the visualization of body structures or vasculature. To date, FDA has approved seven GBCAs. The agents contain gadolinium, a paramagnetic metal which must remain chelated within the agent to avoid toxic effects from the gadolinium.

In 2006 NSF, a scleroderma-like disease, was associated with the use of GBCAs among patients with severe renal insufficiency. Further observational studies have found that NSF produces characteristic skin lesions and a fibrotic process within multiple body organs which may result in death.

In 2006 and 2007, FDA issued a series of communications pertaining to the risks for NSF in association with GBCAs. In 2007, following FDA requests, manufacturers of the agents revised their labels to include a boxed warning and other information intended to lessen the risk for NSF. The approved labeling text was the same for all the agents since FDA regarded a risk to exist for all the agents. However, the approved label text also noted that "The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents." Additional data have accumulated since the 2007 labeling alteration and this advisory committee will be asked to consider these data, in the context of further labeling alterations or other risk reduction efforts.

Although the GBCAs are viewed as a "class" based upon the same pharmacologic mechanism of action, the agents uniquely differ in multiple aspects (e.g., pharmacokinetics, pharmacodynamics, potential risk for anaphylaxis, etc). In this regard, FDA-approved labeling based upon a "GBCA class effect" does not indicate that all members of the class have identical risks nor does it mean that the magnitude of any individual risk (e.g., NSF) is the same for all members of the class. Instead, the "class" risk indicates that the potential for the risk exists among all members of the drug class.

Beyond the concept of a pharmacologic "class," GBCAs have been categorized in various ways, e. g, by their molecular structure, thermodynamic stability, indication, etc. One of the most common categorizations is based upon the drugs' molecular structures and propensity for liberation of gadolinium. Specifically, three groups have been identified: linear, non-ionic; linear, ionic; and macrocyclic. Various *in vivo* and *in vitro* studies have strongly suggested that these categories help support the theoretical role of "transmetallation" in the pathogenesis of NSF. Data appear to indicate that the "linear, non-ionic" agents, more so than the other molecular groups, tend to liberate gadolinium leading to “free” NSF-producing gadolinium in contact with body organs. The "linear ionic" agents are reported to have an intermediate propensity for liberation; the macrocyclic agents reportedly “cage” gadolinium and have the least propensity for transmetallation. The risk for NSF has been proposed to vary based upon the specific structural/transmetallation category.

Most GBCAs are eliminated from the body via renal excretion. In patients with renal insufficiency, GBCAs may remain within the body for a prolonged period of time, potentially increasing the risk for NSF. Conceivably other patient-specific characteristics, such as concomitant medications, may impact the risk for NSF. These observations exemplify the many factors important to consider when estimating the risk for development of NSF. Additionally, available data suggest that the dose of a GBCA (either as a single administration or the cumulative dose from repetitive administrations) represents an important consideration in the risk for NSF. Hence, the specific GBCA alone may not represent the single most important risk factor for NSF. Other considerations (dose, patient characteristics) may also importantly impact the risk.

The FDA has recently completed a data review that recommended enhancement of the GBCA labeling to indicate a comparatively greater risk of NSF for certain agents (Omniscan, Magnevist and Optimark). However, the data do not appear to rule out an NSF risk for each of the agents. Indeed, multiple considerations (other than the specific GBCA) may importantly contribute to the risk for NSF. The appropriateness of concluding that the GBCAs differ in the risk for NSF is one of the topics for the committee's discussion. If the committee regards the data as indicative of a difference in risk, FDA anticipates asking for advice on how best to describe this differential risk within labeling (or other communications).

While NSF is the focus of this committee's discussion, labeling and risk communication discussions must also involve considerations of the other risks associated with GBCAs, such as the risks for hypersensitivity reactions (including fatal anaphylaxis) and acute renal failure. An overall NSF communication strategy must consider the appropriate level of emphasis or de-emphasis of the risk, particularly considering the potential for misinterpretation of the information, i.e., a drug perceived as "safe" or "unsafe" based upon consideration of only the NSF risk.

Introduction

GBCAs are administered in conjunction with MRI procedures to improve the diagnostic capabilities of MRI. Since 2006, an association has been recognized between GBCAs and the development of NSF. NSF is a systemic fibrosing syndrome that is thought to occur predominantly in patients with severe renal insufficiency. NSF is defined by the development of relatively characteristic skin lesions (confirmed by skin biopsy) and internal organ fibrosis which may lead to organ failure.

Seven GBCAs are currently on the USA market; five were present at the time NSF was initially associated with GBCA in 2006. These five agents have been administered to millions of patients although precise estimates of GBCA exposure are very limited. For example, the agents have historically held unequal market shares. Additionally, some patients undergo exposure to more than one agent. These limitations complicate estimates of GBCA exposure and NSF prevalence analyses.

This Briefing Document will focus on the five GBCAs marketed in 2006: Omniscan, Optimark, Magnevist, Multihance, and Prohance. The GBCAs introduced since then, Vasovist and Eovist, have reportedly had comparatively small patient exposure.[1] Hence these two newer agents do not provide significant new information concerning NSF.

In a response to the initial reports of NSF, FDA published two Public Health Advisories and other communications on the FDA website. In 2007, FDA approved labeling for all the marketed GBCAs to describe the NSF risk and potential ways to minimize the risk. The same labeling text was approved for all agents. Presentations at the advisory committee and contained within this Briefing Document should help guide the committee as they consider the questions posed by the FDA.

Purpose of the Advisory Committee

Following presentation of data by guest speakers, companies and the FDA staff, FDA anticipates a discussion of the factors important in assessing the risk for NSF in association with GBCAs. FDA is particularly interested in opinions regarding differences in the magnitude of risks among the agents and, given differences, how best to describe this information in labeling or other communications.

Presentations are planned to consist of a brief discussion of the chemical characteristics of the GBCAs and nonclinical data; a review of usage data from the sponsors along with other agent-specific considerations; epidemiologic data on NSF occurrence and a review of the NSF clinical studies in the medical literature. None of the individual data sources provide a clear, unambiguous picture as to the fundamental question of differential NSF risk among the marketed GBCAs.

Specifically the committee will be asked to weigh all of the presented data and render opinions concerning:

- The applicability of chemical characteristics to the assessment of NSF risks;
- The interpretation of post-marketing exposure/case incident data;
- The difference in NSF risks among the GBCAs;
- The most appropriate methods to screen patients for renal impairment prior to administration of a GBCA;
- The most appropriate approach to communicating NSF risks and risk minimization measures;
- The potential for conducting studies intended to more precisely estimate NSF risks.

[1] The USA trade names of these products will be used throughout this briefing document. See table 1 for the corresponding chemical names.

Background Information on the Gadolinium Based Contrast Agents

GBCAs are gadolinium chelates (large organic molecules which bind gadolinium); the specific molecular structures and chemical bonding vary among the agents. Gadolinium is a lanthanide metal with paramagnetic properties due to seven unpaired electrons in its outer shell and, in its free ionic form which is necessary for solubility, gadolinium is toxic to humans. This toxicity is overcome through chelation; the formation of a complex with a large organic molecule. This chelation was proposed to render the gadolinium biochemically inert and non-toxic.

Some reports have classified GBCAs into categories on the basis of their chemical structure (linear vs. marcrocyclic) and their charge (ionic vs. nonionic). The physiochemical characteristics of the GBCAs, thermodynamic and kinetic stability, may have important implications for the liberation of Gd^{3+}, a process called transmetallation, and possible subsequent toxicities. Macrocyclic chelates are proposed to bind Gd^{3+} more tightly than linear chelates and are proposed to be more stable both *in vitro* and *in vivo*.

In general, the chelates of the GBCAs hold onto the gadolinium ion as it exhibits paramagnetic properties in a strong magnetic field induced by the MRI machine. Gadolinium contained in the GBCA alters the relaxation times (the way paramagnetic substances react in magnetic fields) of tissues and body cavities. Depending on the image weighting (T values used to highlight different tissues), the tissue surrounded by a GBCA will emit a higher or lower radio signal detectable by the MRI device. Most MRI contrast agents work through shortening the T1 or T2 relaxation time of protons located nearby. Reduction of T1 relaxation time results in a hypersignal while reduced T2 relaxation time reduces both T2 and T2* signals. These differential signals are translated by the MRI into black and white images based on the signal characteristics.

History of Use

Magnevist was the first FDA-approved GBCA (1988). Since that time six other GBCAs have been approved. The agents are used extensively use in MRI (Magnetic Resonance Imaging) of the CNS and other body compartments. One GBCA (Vasovist) is FDA-approved for use in MRA (Magnetic Resonance Angiography); the other agents are sometimes used in MRA although they are not approved for this purpose. These "off label" MRA uses may involve GBCA doses that exceed those recommended for MRI.

Table 1: GBCAs marketed in the United States

Agent	Established Name	Company	approval date	NDA#	Indication	Structure	Notes
Magnevist	gadopentetate dimeglumine, Gd-DTPA	Bayer	06/02/88	019596	CNS, Extra Cranial, Extra-Spinal, Body*	Linear ionic	
Magnevist	gadopentetate dimeglumine, Gd-DTPA	Bayer	03/10/00	021037-pharmacy bulk			
ProHance	gadoteridol, Gd-HP-DO3A	Bracco	11/16/92	020131	CNS, Extra Cranial, Extra-spinal	Macrocyclic	
ProHance	gadoteridol, Gd-HP-DO3A	Bracco	10/09/03	021489-multipack			Repeat dose may be given
Omniscan	gadodiamide, Gd-DPTA-BMA	GE	01/08/93	020123	CNS, Body*	Linear non ionic	Repeat dose may be given
Omniscan	gadodiamide, Gd-DPTA-BMA	GE	09/05/07	022066-pharmacy bulk			
OptiMark	gadoversetamide, Gd-DPTA-BMEA	Mallinckrodt	12/08/99	020937	CNS, Liver	Linear non ionic	
OptiMark	gadoversetamide, Gd-DPTA-BMEA	Mallinckrodt	12/08/99	020975			
Optimark	gadoversetamide, Gd-DPTA-BMEA	Mallinckrodt	12/08/99	020976-plastic container			

Agent	Established Name	Company	approval date	NDA#	Indication	Structure	Notes
MultiHance	gadobenate dimeglumine, Gd-BOPTA	Bracco	11/23/04	021357	CNS, Spine	Linear ionic	
MultiHance	gadobenate dimeglumine, Gd-BOPTA	Bracco	11/23/04	021358-multipack			
Eovist	gadoxetate disodium, Gd-EOB-DTPA	Bayer	07/03/08	022090	Liver	Linear ionic	Primovist in the countries of the EMEA
Vasovist	gadofosveset trisodium	Epix (now Lantheus)	12/22/08	021711	Aortic-iliac Occlusive Disease	Linear ionic	Ablavar proposed new name

* Intrathoracic, (noncardiac), intra-abdominal, Pelvic and Retroperitoneal Regions

MRI has achieved considerable clinical usage and GBCAs have been administered to millions of patients. MRI with GBCA has been regarded as an important diagnostic imaging procedure, critical to the diagnosis of multiple conditions. In some situations, MRI with GBCA has been regarded as an important alternative to computerized tomography (CT) because of improved visualization with MRI and its lack of radiation exposure. Additionally, MRI with a GBCA has been regarded, in many situations, as an alternative to the use of CT with a contrast agent in patients intolerant to iodinated agents (e.g., due to underlying renal impairment). Currently however, data suggest that GBCAs may increase the risk for renal impairment, particularly in patients with underlying renal disease (CKD).[2,3]

Among the marketed GBCA agents, the indications differ, as listed in table 1. Magnevist and Omniscan carry an indication for imaging of multiple body regions while most of the other GBCAs are limited to indications for neck and CNS visualization. Additionally, Omniscan and Prohance are labeled to allow a second higher dose to be given in order to optimize CNS imaging.

All of the GBCAs are excreted through the kidneys with relatively short half lives in patients with normal renal function; renal insufficiency prolongs the exposure to gadolinium. The majority of GBCAs have a serum elimination half-life in the 1-2 hour range in the healthy human. Vasovist has an extended mean elimination half-life of 18.5 hours; ~10 times longer than for all other GBCAs, perhaps related to its binding to plasma albumin. The recommended dose for Vasovist is 0.03 mmol/kg which is 3-10 times lower than for all other GBCAs except for Eovist (0.025 mmol/kg). The relaxivity properties of these two new GBCAs appear to permit adequate imaging with a lower dose of gadolinium.

Vasovist can also be eliminated via bile (≤9%), a property shared with Eovist which has biliary elimination to a much greater extent (50%). Both Vasovist and Eovist also have a narrow indication spectrum: MRA for Vasovist; liver lesion detection and characterization for Eovist. Serum elimination half-life for Eovist increases to a lesser extent than for some other GBCAs tested (Magnevist and Multihance) in end-stage renal failure patients.

History of Nephrogenic Systemic Fibrosis (NSF)

Clinical Characterization of NSF

In 2000, somewhat coincident with the increased usage of GBCA in angiographic imaging procedures, a report appeared in the literature of what initially was thought to be a new scleroderma skin condition. The syndrome was initially named nephrogenic

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[2] Perazella, M, Current Status of Gadolinium Toxicity in Patients with Kidney Disease, Clin. J. Am Soc Neph 2009; 4: 461-9.
[3] See Addendum for the definition of the stages of chronic kidney disease

fibrosing dermopathy (NFD): There were characteristic skin lesions, sparing of the face and no serological correlates. Affected patients developed large areas of hardened skin with slightly raised plaques, papules or confluent papules; with or without pigmentary alteration. All 15 cases of NFD had occurred in renal dialysis patients; the first cases were identified as occurring in 1997.[4]

Further reports by 2005 revealed involvement of the pleura, pericardium, lungs, joints, diaphragm, and myocardium. The syndrome was potentially lethal through cardio-respiratory failure. In recognition of the systemic involvement, the name was changed to Nephrogenic Systemic Fibrosis (NSF).

NSF appears to affect males and females in approximately equal numbers; has been confirmed in children and the elderly and identified in patients with a variety of ethnic backgrounds. The age range has spanned patients from 8 to 86 years old. Besides severe kidney disease either with or without hemo- or peritoneal dialysis, conditions that may be associated with NSF include coagulation abnormalities, deep venous thrombosis and recent surgery.

A registry has been initiated by Dr. Cowper at Yale University to develop uniform diagnostic criteria and to obtain follow-up information about patients with NSF.[5] Dr. Cowper presented clinical-pathologic criteria for making the diagnosis of NSF at the Third Annual Scientific Symposium on Nephrogenic Systemic Fibrosis and MR Gadolinium-based Contrast Agents held in May, 2009[6]. He proposed that, in addition to characteristic findings on microscopic examination of the skin biopsy, CD34+ cells should be present. These cells are proposed to be form of a circulating fibrocyte. The classification also takes in account clinical findings from a physical examination. These criteria have been widely accepted and are employed in the post-marketing trials currently underway by the GBCA manufacturers.

Several experimental treatments for NSF have been proposed including steroids, chemotherapeutic agents, extracorporeal plasmapheresis and photopheresis; however to date no treatments have been consistently successful. Some patients with NSF (estimated at 5% or less) have an exceedingly rapid and fulminant disease course that may result in death. NSF, by itself, is not a cause of death, but may contribute to death by restricting effective ventilation or leading to trauma through a fall or other mishap.[7]

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[4] Cowper, SE, Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet 2006; 356:1000-1

[5] International Center for Nephrogenic Fibrosing Dermopathy Research website (http://www.icnfdr.org/)

[6] Yale Center for Continuing Medical Education

[7] International Center for Nephrogenic Fibrosing Dermopathy Research website (http://www.icnfdr.org/)

Investigation of the Relationship of NSF to GBCA Administration

Preclinical Studies

Studies have attempted to model the development of NSF in animals; for example, the administration of comparatively high GBCA doses (relative to human doses) to partially nephrectomized rats. Some studies have examined comparatively high doses in healthy animals. Multiple studies are present in the literature; highlights of three representative studies (including an *in vitro* study) are presented here, including excerpts from the publication abstracts.

In one study of partially nephrectomized rats (5/6 nephrectomy), the animals were injected once daily for 5 consecutive days with a GBCA (Omniscan, Optimark, Magnevist or Gadovist) at a dose of 2.5 mmol/kg. Skin biopsies were taken at various time points and the gadolinium concentration was determined in the tissue. The authors reported differences in the skin gadolinium concentrations among the 4 tested agents. For the nonionic linear compounds, Omniscan and Optimark, "high gadolinium concentrations were maintained in the skin over the observation period of up to 168 days post injection. For the ionic liner compound, Magnevist, comparatively lower gadolinium retention in the skin was observed over time. For the macrocyclic compound, Gadovist, the gadolinium values in the skin were even lower and significantly lower than gadolinium values in the skin in Omniscan and Optimark-treated animals." However, the authors noted that the analytical method for gadolinium determination in the tissue did not distinguish between chelated and unchelated gadolinium.[8]

A study by Sieber examined the effect of "high dose" GBCA (Omniscan, Optimark, Magnevist, MultiHance, Gadovist, and Dotarem) administration to healthy male rats.[9] The rats received repeated intravenous injections of six different GBCAs at "high doses to simulate the exposure seen in patients with severe renal dysfunction. Histopathological and immunohistochemical analysis of the skin was performed and the concentrations of gadolinium, zinc and copper were measured in several tissues..." The authors report that histopathologic changes "similar to those seen in NSF patients were only observed in rats receiving Omniscan. In addition, very high concentrations of gadolinium were observed in the animals treated with Omniscan and, to a lesser extent, in animals treated with Optimark. Significantly lower levels of gadolinium were found after the treatment with ionic linear agents and even less after the treatment with macrocyclic agents."

A study reported by Frenzel et. al. examined the stability of certain GBCA in human sera (ph 7.4, 37^{o} C).[10] The kinetic profiles of gadolinium ion (Gd3+) dissociation of GBCAs was determined by incubation for 15 days in sera from healthy volunteers at a concentration of 1 mmol/L. Additionally, "in an attempt to simulate the situation in

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[8] Pietsch et al Invest Radiol 2009; 44: 226
[9] Sieber et al Eur Radiol 2008; 18:2164
[10] Frenzel, Invest Radiol 2008;43:817.

patients with end-stage renal disease who often have elevated serum phosphate levels, the influence of 10 mmol/L phosphate on Gd3+ dissociation was also investigated." After 15 days the release of gadolinium ion from the linear, non-ionic GBCAs (Omniscan 20%, Optimark 21%) was at least 10 times higher than that from the linear ionic GBCAs (Magnevist, Multihance, Vasovist and "Primovist" also known as Eovist) which ranged from 1-2%. Elevated serum phosphatase levels accelerated the release of rate of gadolinium ion from linear, non-ionic GBCAs (by nearly 100 fold) and to a lesser degree, from the linear, ionic GBCAs, 12-30 fold.

Clinical Studies

In 2006, Grobner reported that 5 out of 9 patients with end stage disease undergoing MRA developed skin changes of NSF about 2-4 weeks after the administration of a gadolinium containing contrast agent (Gd-DTPA-BMA). Dr. Grobner suggested that GBCA may play a triggering role in the development of NSF under certain circumstances[11].

At approximately the same time, the Danish Medical Agency reported a cluster of 20 cases of NSF in patients with severe renal impairment all of whom had received Omniscan. Five cases of NSF were reported from Austria, also in patients with severe renal impairment who had received Omniscan.

In the United States, the CDC reported on a cluster of 33 patients who were undergoing dialysis and who were also diagnosed with NSF. The CDC analysis showed an association between NSF and GBCA exposure generally during the preceding 6 months or preceding year. Five case patients had no identified GBCA exposure within 1 year preceding NSF diagnosis; 4 had GBCA exposure from 16-68 months preceding diagnosis; the fifth had no evidence of GBCA exposure.[12]

Multiple other studies have reviewed GBCA use at imaging centers and the occurrence of NSF. These literature reports will be reviewed in the OSE section of this Briefing Document.

Clinical Presentations

In the majority of reported cases, symptoms have developed within approximately 2 months of the suspect administration of a GBCA. Cowper et. al. reported on the clinical findings of 130 patients from the literature as well as from his personal experience at Yale University.[13]   In this publication, the authors report the "typical clinical course of NSF." According to the authors, the clinical course begins with swelling of the distal extremities; 32% of patients will have edema beyond their baseline. "When edema is present it can resolve, leaving firm plaques that progress to more extreme induration and

[11] Grobner,T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis, Neph Dial Trans Vol 21, Number 4 pp 1104-1108
[12] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5607a1.htm
[13] Cowper, S. Clinical and histological findings in nephrogenic systemic fibrosis, EJR 2008: 66; 191-199.

thickening of the affected skin. Some patients may present with deep NSF skin lesions relatively early and rapidly, and conversely, more superficial lesions may appear on patients long after established, deep involvement has occurred." The authors also note that, in the majority of NSF patients, the earliest lesions appear on the lower extremities, followed by the upper extremities and the trunk. "The skin involvement is often symmetrical and bilateral. Skin lesions are localized in decreasing order of frequency to the lower extremity (85%), upper extremity (66%), trunk (35%), hands (34%), feet (24%), buttocks (9%) and face (3%)." Others have reported that some skin lesions may be papules and coalescing plaques localized to the extremities and torso creating an appearance suggestive of the skin of an orange (known by the French term *peau d'orange*). These lesions reportedly have a wooden like consistency.

Reportedly, in the majority of patients with NSF, symptomatic skin lesions were the initial manifestation of the disease. Associated symptoms are listed in Table 2 below. Other reported symptoms were weakness, palpable warmth and causalgia. Several patients have described costochondral pain.

Eye findings which are seen in a large proportion of NSF patients consist of white-yellow colored plaques with telangiectatic vessels located on the sclerae.[14] Patients may go on to develop fibrotic changes within multiple internal organs leading to severe dysfunction.

Table 2: Adopted from European Journal of Radiology (EJR) 2008

NSF cutaneous symptoms	
Pruritus	36%
Burning	16%
Pain	52%
Tightness	30%
Swelling	25%
Paresthesia[a]	24%
Joint stiff	34%

[a] Includes tingling, numbness, and/or prickling sensations.

[14] Cowper, S. J Am Col of Rad 2008; 5: 23-28.

(b) (4)

(b) (4)

[redacted]

(b) (4)

Case Reports

The FDA receives reports on possible NSF cases from a variety of sources including the Medwatch reporting system which allows medical professionals, and the general public including patients, families, and lawyers to initiate reports.[15] Content within the reports can vary widely. To exemplify the difficulties in interpreting these reports, an example is presented below:

The 2008 report, supplied by an attorney, pertained to a male patient (age not reported). The patient had renal insufficiency. "It is unknown whether any concomitant drugs have been given. Upon information and belief, the patient was administered Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide), Optimark (gadoversetamide), MultiHance (gadobenic acid meglumine) and/or Prohance (gadoteridol) for MRI (unspecified) in 2005." Exact administration dates and total doses given were not reported. "After being administered Magnevist, Omniscan, Optimark, MultiHance, and/or

[15] http://www fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm

Prohance, the patient developed NEPHROGENIC SYSTEMIC FIBROSIS (NSF, considered serious due to medical significance)... As a direct and proximate result, the patient suffers from debilitating and worsening fibrotic changes; serious, progressive, permanent, incurable injuries; significant harm; physical injury; pain; bodily impairment; disfigurement and scarring; conscious pain and suffering, emotional distress, emotional injury; and physical limitations." No additional details were supplied.

Several other case reports will also be presented in the OSE section of this Briefing Document.

FDA Response

The FDA learned of 25 cases of NSF reported on May 29, 2006, by the Danish Medicines Agency. Among these, 20 cases occurred in Denmark and 5 cases occurred in Austria; all of the patients received Omniscan. The 5 patients from Austria were described in a publication[16]. In reaction to this information, The FDA issued a Public Health Advisory (PHA)[17]. The recommendations made then:

- GBCA, especially at high doses, should be used only if clearly necessary in patients with advanced kidney failure- those on dialysis or with a glomerular filtration rate (GFR) = 15 ml/min or less.
- "It may be prudent to institute prompt dialysis in patients with advanced kidney dysfunction who receive a gadolinium contrast MRA."

In an "Information for Healthcare Professionals" issued at the same time, the FDA noted that none of the GBCAs are approved for Magnetic Resonance Angiography (MRA) where the administered dose can be up to three times higher than the approved dose for contrast MRI. The FDA also posted on its public website Questions and Answers concerning GBCAs.[18] The FDA explained that the link between GBCAs and NSF was not conclusive.

Later in 2006, the FDA issued another series of public communications[19]. FDA reported the receipt of reports for 90 patients with moderate to end-stage kidney disease who developed NSF after an MRI or MRA. "Many, but not all of these patients, received a higher dose of the GBCA, some received only one dose." The GBCA involved were Magnevist, Optimark and Omniscan. In the accompanying Information for Healthcare Professionals, the FDA urged cautious use in patients with a GFR from 60 mL/min to end

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[16] Grobner, T Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis, Nephrol dial Transplant. 21(4): 1104-8
[17] http://www fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm053112 htm
[18] http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142907.htm)
[19] http://www fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm124344 htm

stage kidney disease. In the web-posted Questions and Answers the FDA noted that the finding of gadolinium in the skin of patients with NSF suggested that GBCA is a factor in the development of NSF in patients with moderate to end stage kidney disease.
In May, 2007, following the accumulation of more data and an internal review at FDA, labeling changes were made to all United States marketed GBCAs: Each GBCA label was to carry a boxed warning as well as additional information in the "warnings" section, as highlighted below.

The boxed warning:

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:

- acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2), or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration (See WARNINGS).

From the Warning Section of the label for each GBCA:

"**Nephrogenic Systemic Fibrosis (NSF)**

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced MRI. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a gadolinium-based contrast agent in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a gadolinium-based contrast agent and the degree of renal function impairment at the time of exposure.

Post-marketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following sequential administrations of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific gadolinium-based contrast agent.

The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimate risk for development of NSF was 4% (J Am Soc Nephrol 2006;17:2359). The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any readministration. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION)."

FDA Regulatory Considerations

FDA considers the GBCAs to be part of a single pharmacologic class because all of the agents fulfill at one of the three attributes noted in the guidance to meet the definition of a pharmacologic class:[20]

1. Mechanism of action – paramagnetic properties of Gadolinium
2. Physiologic effect
3. Chemical structure

Additionally the Guidance defines an established pharmacologic class by a term or phrase that is scientifically valid and clinically meaningful according to the following definitions:

- A *scientifically valid* pharmacologic class is supported by documented and submitted empiric evidence showing that the drug's pharmacologic class is known, not theoretical, and relevant and specific to the indication.

[20] Guidance for Industry and Review Staff: Labeling for Human Prescription Drug and Biological Products – Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm

- A *clinically meaningful* pharmacologic class term or phrase enhances the ability of professionals to understand physiologic effects related to the indication or to anticipate undesirable effects that may be associated with the drug or pharmacologic class.

Hence based on these criteria the GBCA meet the criteria of a class.

At the label change alteration in 2007, FDA requested manufacturers to add extensive information to the "warnings" section of their labels. One of the considerations for labeling involved a potential addition to the "contraindications" section of the label. In the December 8, 2009 Committee's discussions of differential risks among the agents and the potential for additional label changes, the FDA guidance on "contraindications" is relevant. The guidance definition is stated below:

A drug should be contraindicated only in those clinical situations for which the risk of use clearly outweighs any possible clinical benefit.[21]

Additional Regulatory Actions

In addition to the label changes in 2007, each GBCA manufacturer was requested to perform a postmarketing clinical trial of their agent in patients with moderate to severe renal insufficiency in order to assess the magnitude of NSF among these patients. FDA subsequently modified these agreed-upon trials to "post-marketing requirements," based upon newer legislation. Each trial was to enroll 1000 patients; 600 with moderate renal insufficiency having a GFR < 60 ml/min and 400 with severe renal insufficiency and thus with a GFR<30 ml/min. Omniscan has not presented a final protocol for studying patients with a GFR < 30, the Vasovist protocol is under review with the FDA and Optimark has not enrolled any patients its study. The other sponsors are enrolling patients in their studies.[22]

Actions by Other Regulatory Authorities: EMEA

The Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP), a branch of the EMEA, held initial discussions on the risk of NSF and GBCA(s) in June, 2006. A Direct Healthcare Professional Communication (DHPC) was circulated to warn of the GBCA and NSF association and market authorization holders (MAH) of GBCAs were requested to submit extraordinary Periodic Safety Update Reports (PSUR) to identify similar cases with their products.
In December, 2007 a Scientific Advisory Group (SAG) convened by the EMEA indicated that the NSF risk of the GBCAs depended on their thermodynamic and kinetic properties and advised categorization of the agents into three groups:

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[21] Human Prescription Drug and Biological Products – Content and Format
http://www fda.gov/cder/guidance/index.htm
[22] http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default htm

- **Low risk:** Marcocyclic chelates: gadoterate megulmine (Dotarem, not available in the United States), gadoteridol (Prohance) and gadobutrol (Gadovist not available in the United States)
- **Medium risk:** Linear ionic chelates: gadofosveset trisodium (Vasovist, now called Ablavar in the United States), gadoxetic acid disodium (Primovist, called Eovist in the United States), and gadobenate dimeglumine (Multihance)
- **High risk:** Linear non-ionic chelates: gadoversetamide (Optimark) and gadodiamide (Omniscan)
- **High risk**: Linear ionic chelate: gadopentetate dimeglumine (Magnevist)

The rationale for this categorization was further explained in January, 2008 when the PhVWP suggested a mechanism for the development of NSF mentioned earlier in this Briefing Document: These physicochemical properties which form the basis of the categorization affect the release of toxic free gadolinium ion from the chelate contrast agent complex through a process called transmetallation with other endogenous ions within the body. Thus free gadolinium ion is liberated within multiple body organs except the brain. Additionally in severe renal insufficiency with a diminution in renal clearance of the GBCAs, these agents remain in the body for a long time thus creating a prolonged exposure to toxic Gadolinium ion. Based on this concept of NSF development and the categorization outlined above, the PhVWP advised that Omniscan use in patients with severe renal impairment (GFR<30 mL/min) or liver transplantation be strictly contraindicated. In subsequent actions through the EMEA member states similar contraindications were issued for Magnevist and Optimark.

Topics for Questions

FDA anticipates questions and discussions pertaining to the topics outlined below. Each topic is followed by a summary of major background points.

1. The applicability of chemical and physiochemical properties of the GBCAs to the assessment of a difference in the NSF risk for each agent.

    - Some of the GBCAs contain excess chelate to “capture” any free gadolinium dissociated from the gadolinium-chelate complex. The agents differ in the content of excess chelate, suggesting that they also differ in the potential for release of gadolinium.
    - The agents differ in gadolinium-chelate dissociation measures.
    - Other inorganic ions such as Iron and Calcium form a stronger bond with the chelate than does gadolinium.
    - A macrocyclic GBCA reportedly forms a comparatively stronger bond with gadolinium; these agents have been associated with a “low to no” incidence of NSF.

- The applicability of *in vitro* gadolinium-chelate dissociation to the clinical situation has been questioned, due to potential local tissue variations in pH and the metabolic abnormalities associated with renal insufficiency.

2. The applicability of the number and nature of post-marketing NSF reports to the assessment of a difference in the NSF risk each agent.

   - Certain GBCAs have accounted for the preponderance of NSF reports in post-marketing databases.
   - The ability to develop precise estimates of NSF rates (based upon exposure) is very limited. Post-marketing databases have many limitations, such as incomplete information, lack of identification of the suspect agent, uncertain drug doses, report duplication and uncertain diagnoses.
   - Reports of NSF have seemed to occur in clusters. For example, a relatively large number of cases from a single hospital in Denmark and another in the United States.
   - Data regarding specific GBCA exposure have many limitations. Some GBCAs have been on the market much longer than products more recently introduced. The agents differ in their market shares.

3. The overall assessment of important differences in NSF risks among the GBCAs.

   - Knowledge of molecular structure, animal studies, clinical studies and post-marketing reports may impact the overall assessment of risks.
   - Labeling and communications are expected to appropriately describe all the major risks for GBCAs, not solely those related to NSF. Inappropriate labeling for GBCAs may result in a shift in clinical practice toward procedures/drugs that may have even greater risks.
   - A "contraindication" in labeling generally correlates with a determination that in all clinical situations, the risks outweigh any benefit. A "warning" outlines the risk and ways to minimize the risk allowing more prescriber-discretion compared to a "contraindication."

4. The ability to conduct clinical studies among patients at risk for NSF in order to more precisely estimate risks.

   - The occurrence of NSF has appeared to markedly decrease over the last year.
   - Clinical practice guidelines and labeling have encouraged the screening of patients for renal impairment. These efforts may have increased awareness of the NSF risks.
   - Institutions and practices may favor one agent over another, based upon perceived risks and medical practice considerations.
   - A labeling "contraindication" generally precludes use of the agent in any clinical situation and may importantly limit the ability to conduct clinical studies.

5. The most useful method for screening patients for renal impairment or other risk factors for NSF.

    - Current labels recommend screening patients for renal dysfunction based upon "history and/or laboratory tests."
    - In light of the occult nature of renal dysfunction, one of the considerations for screening involves the measurement of renal function (e.g., serum creatinine-based estimate of GFR) among all patients who are to receive a GBCA.

Highlights of the OSE Report

The Office of Surveillance and Epidemiology (OSE) has been monitoring reports of NSF since the disease and its association to NSF surfaced. In preparation for this Advisory Committee, OSE performed a detailed review including; analysis of drug utilization; MedWatch reports; data mining and a literature review.

Analysis of Drug Utilization

By querying various drug distribution databases, OSE found that 7.7 million vials of GBCAs were sold in 2008 which was down from 8.5 million in 2005. Most of the sales were to non-federal hospitals. Magnevist comprised about 50% of the market share in 2008. Omniscan was second in sales but decreased from almost 40% of the market share in 2006 to about 20% in 2008. Multihance showed an increase in sales but comprised only a small part of the market. The other marketed GBCAs have maintained consistent sales and market share. Inpatient utilization data for the GBCAs reflects the general trend in sales data. Unfortunately, a large portion of the exposure data has been reported as "gadolinium" or "unspecified" GBCA. Employing data from hospitals reporting a specific agent showed that Magnevist had the most usage.

MedWatch

MedWatch is a post-marketing reporting system that may include duplicate reports. Below is a list of crude numbers of domestic reports of NSF for each of GBCA. Note that recently approved agents have not been included.

Table 3: Crude numbers of domestic reports of NSF for each GBCA

Product	Year of FDA Approval	Domestic NSF Reports in AERS	Domestic Single Agent NSF Reports in AERS**
Omniscan	1993	929	382
Magnevist	1988	654	195
Optimark	1999	427	35
Prohance	1992	325	0***
Multihance	2004	335	1

Among the MedWatch NSF cases where the GFR was reported in the narrative, only one case reported GFR at the time of GBCA administration that would indicate less than severe renal dysfunction. This suggests that NSF has occurred almost exclusively among patients with severe renal insufficiency.

Data Mining

This analysis identified the highest reporting parameters, Proportional Reporting Ratio (PRR) and Relative Reporting Ratio (RRR), for Omniscan and Optimark.

Table 4: Data Mining analysis: Proportional Reporting Ratio and Relative Reporting Ratio for domestic cases of NSF among GBCAs listed as the primary suspect drug

	Proportional Reporting Ratio (PRR)			Relative Reporting Ratio (RRR)		
	Statistic	Asymptotic 95%CI		Observed /Expected	Observed Count	Expected Count
Drugs of interest	PRR	LB	UB	RRR of GPS	OC	EC
Magnevist	0.780	0.697	0.873	0.888	530	597.03
Prohance	0.021	0.010	0.044	0.027	7	255.38
Omniscan	7.192	6.506	7.950	4.537	464	102.28
Optimark	5.406	4.585	6.375	5.109	73	14.289
Multihance	0.064	0.032	0.128	0.071	8	113.02

Literature

Omniscan appeared to be associated with an estimated higher prevalence of NSF compared to Magnevist, Multihance and Optimark in the majority of studies evaluated. However, most of the studies had significant limitations that affected the validity and the ability to generalize from the results. Reports noted that there may be a dose-response relationship between GBCAs exposure and NSF. Specifically, reports indicated that the likelihood of developing NSF appeared to increase with either a single high dose or high lifetime dose.

Overall Conclusion

Omniscan, estimated to be the second most commonly used GBCA, has been associated with the most reports of cases of NSF. Reports have been received for several other GBCAs. However issues such as multiplicity of dosing and off label use confound any ability to calculate accurate rates of risk for each of the GBCA.

Highlights of the FDA Review of the Sponsor’s Answers to the Information Request Letter Regarding the Current Usage of their GBCA

FDA Request 1a. Provide summaries and analyses of the most recent cumulative findings from the prospective observational study you established under an FDA Postmarketing Commitment (PMC) described in 2007.

The sponsors provided an update indicating that the trials were enrolling. Vasovist, a newer GBCA, has submitted a final protocol to the FDA. The Optimark manufacturer reported that they could not recruit more than one site and patient enrollment had not begun. Omniscan as mentioned earlier has split its trial into a separate moderate and severe renal insufficiency protocol. The protocol for a trial in patients with severe renal insufficiency has not yet been submitted to the FDA

FDA Request 1b. Provide summaries and analyses of postmarketing reports of NSF from your pharmacovigilance database.

A total 1161 cases have been reported to regulatory authorities around the world. Omniscan had the most with 611 cases, followed by Magnevist with 455 and Optimark with 70 cases. Among the issues limiting the usefulness of this reported data is variable definition of a reportable case; lack of consistent criteria until 2009 for the diagnosis of NSF; an undetermined number of duplicate reports; lack of dosing information; and lack of information concerning renal function testing.

FDA Request 1c. Provide summaries and analyses of drug utilization data for your GBCA.

Companies other than Bayer reported estimates of the number of vials or units sold since their international birth date. Bayer provided estimates of the number of procedures for which their products was used. Magnevist was the first GBCA to be approved internationally and has been administered more times than any other GBCA by at least 2 fold.

FDA Request 1d. Provide summaries and analyses of published literature and provide a summary of NSF reports implicating your GBCA.

The sponsors provide references where their agent is mentioned.

FDA Request 1e. Provide summaries and analyses of outcome data on patients with a confirmed diagnosis of NSF following administration of your GBCA.

For patients who have not died from NSF some have improved while most have not resolved or worsened. No treatment resulted in consistent improvement of NSF.

FDA Request 1f. Provide summaries and analyses of reports of NSF in your phamacovigilance database summarized by six month increments for both event date and reporting date.

The decline in the number of cases with event dates in recent years has been attributed by the sponsors to the boxed warning, increased awareness of NSF and screening for renal impairment.

FDA Request 1g. Provide summaries and analyses of your global experience as well as the subset experience within the United States.

Of the two GBCAs with the most reportable NSF cases, there have been more reportable NSF cases for Omniscan than for Magnevist in the US apparently despite fewer procedures being performed with Omniscan than with Magnevist. For the three GBCAs (Omniscan, Magnevist, and Optimark) with the highest number of reportable NSF cases, the number of cases with event dates within each half year rose from 2000 to 2006 or 2007, and these increases parallel the rise in the use of these particular GBCAs.

FDA Request 2. With respect to the risks, pathophysiologic basis, or both for NSF, provide an overview of toxicology data from humans and animals based upon your product's development program and from the published reports of experiences with your GBCA.

Bayer sponsored studies in rats with decreased renal function and found that Omniscan, unchelated gadodiamide (the drug substance of Omniscan) and unchelated gadoversetamide (the drug substance of Optimark) could produce skin lesions that shared macroscopic and microscopic characteristics with human NSF. GE Healthcare's independent pathology peer review of the original slides from the Bayer sponsored study concluded that the skin lesions are consistent with skin trauma.

FDA Request 3. Describe your plans for any further studies and labeling changes based on the results of your analyses.

Bracco is conducting a study to determine the incidence of NSF in patients with Stage 4 or 5 chronic kidney disease with exposure to GBCAs in the past 10 years. Covidien is conducting a study in rates to investigate the effects of various phosphorus levels on gadolinium deposition follow repeated doses of GBCAs.

FDA Request 4. Multiple GBCAs are currently marketed. Comment upon the factors involved in any differential risks for NSF among these products. Specifically comment upon the factors that you regard as important in distinguishing the risks for NSF with your product in comparison to other products.

Each GBCA sponsor put forth ways to distinguish themselves based on chemical stability differences, pharmacokinetics, nonclinical studies, and clinical studies. The sponsors of Vasovist and Eovist made note that their agents have a component of hepatic metabolism which may lessen the extended half life of their GBCA in the end-stage renal failure patient.

Overall Summary of the Sponsors' Responses

The sponsors supplied usage data in a variable manner. Sponsors other than Bayer provided data on the number of vials sold while Bayer provided data on the procedures performed. Additionally limited data was provided on repetitive dosing and off label use.

These limitations confounded attempts to draw uniform conclusions regarding differential risk of NSF among the GBCAs.

Addendum

Stages of Chronic Kidney Disease[23]

Stage	**Description**	**GFR mL/min/1.73 m^2**
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 (or dialysis)

[23] Adapted from: http://www.kidney.org/professionals/KDOQI/guidelines_ckd/Gif_File/kck_t10.gif

Chemistry Briefing Document

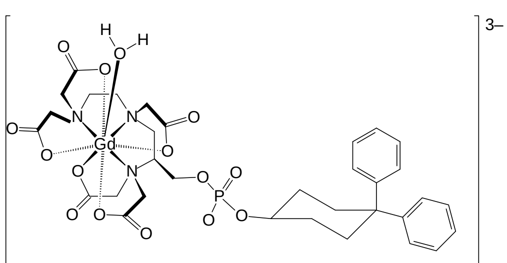
D. A. Place

Joint Meeting of the Cardiovascular and Renal Drug and Risk Management Advisory Committees

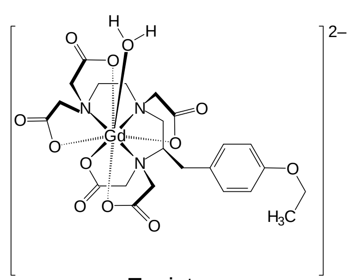
– December 8, 2009

Introduction – Despite the clinical usefulness of Magnetic Resonance Imaging, when the technique became available commercially, it was evident that a contrast medium would make the imaging modality even more powerful. Various magnetic particles and chemical entities were developed by various pharmaceutical companies.

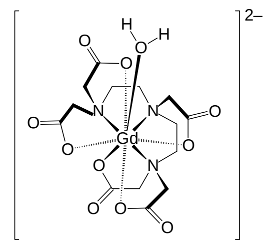
Gadolinium Agents – By far, the most widely used MRI contrast agent drugs are based on the +3 ion of the rare earth metal gadolinium. There are currently seven gadolinium agents approved by the FDA, depicted below. Counterions, where applicable, are omitted.



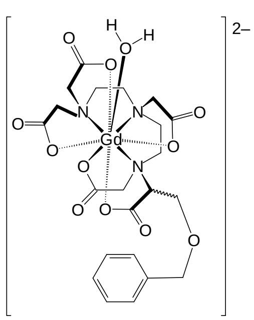
Ablavar



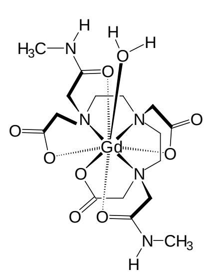
Eovist



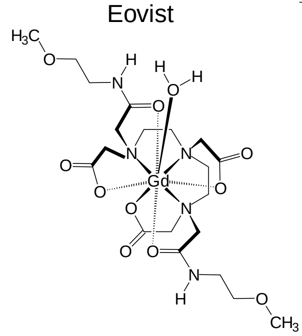
Magnevist



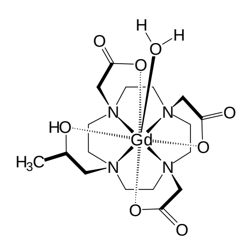
Multihance



Omniscan

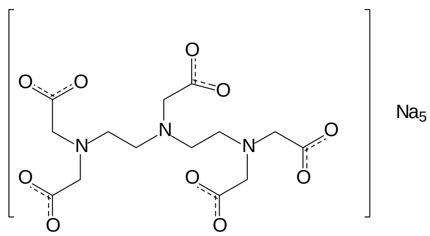


Optimark



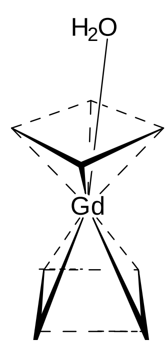
Prohance

Gadolinium(III) has the largest number (7) of unpaired electrons of any metal ion. It is an efficient relaxation agent, which means the hydrogen nuclei in water and tissue return to their ground state faster following MRI excitation than without a paramagnetic agent present. This not only reduces total scan time but also improves tissue contrast in a variety of applications. Another advantage to the use of gadolinium is that it does not cause image shifting and distortions like other lanthanide ions. The problem with gadolinium is that it is toxic unless it is well designed into stable coordination complexes and properly formulated. All of the approved gadolinium complexes share the same complex geometry around the central metal core. The octadentate ligands (like DTPA in Magnevist) wrap around the metal and provide eight points of contact through ionic bonding.



Sodium DTPA

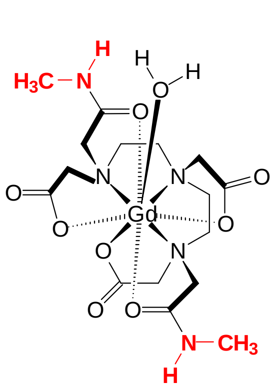
However, gadolinium is nine–coordinate, and this leaves one site for binding to a water molecule, which is rapidly exchanging with other water molecules (millions of exchanges per gadolinium per second). This fast exchange greatly enhances the efficiency of the relaxation process, sharpening the signal and hence enhancing the utility of the agents. Although it is possible to synthesize ligands with more that eight donor atoms, and these metal complexes are more stable, blocking the ninth site eliminates the water exchange and reduces the relaxivity (power to relax) from what is found with the approved agents.



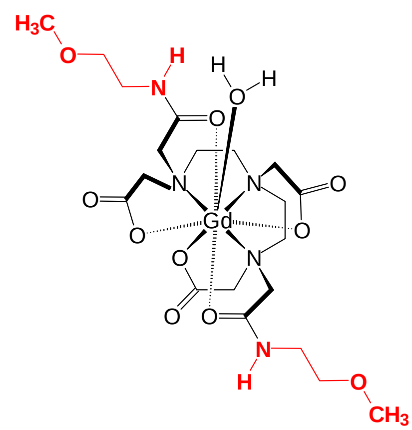
Gadolinium (III) Coordination Sphere

Gadolinium Agents Classification – There are three groups of gadolinium binding agents based on the chemical charge and structure of the attached ligands. The in–vitro stability correlates with the apparent reaction rate of gadolinium decomplexation in vivo.

Linear Non–Ionic – Omniscan (gadodiamide) and OptiMark (gadoversetamide) are based on the linear DTPA structure but where two terminal acetate groups have been converted to amides. Binding of anionic acetates is much stronger than amides. However, since no positive counterions (the aminosugar meglumine or sodium are commonly used) are necessary to balance the complexes charge, the drug product osmolality is lower than those formulated with linear ionic complexes..

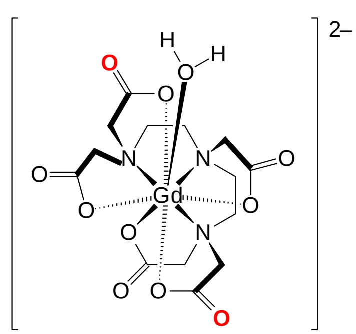


Gadodiamide (Omniscan)



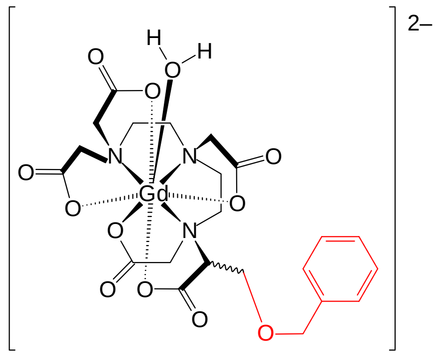
Gadoversetamide (Gadoversetamide)

Linear Ionic – This group includes Magnevist (gadopentetate), the first approved gadolinium contrast agent. Since the DTPA ligand bears five anionic acetate groups, the resulting complex bears a net –2 charge, which is offset by two meglumine cations.

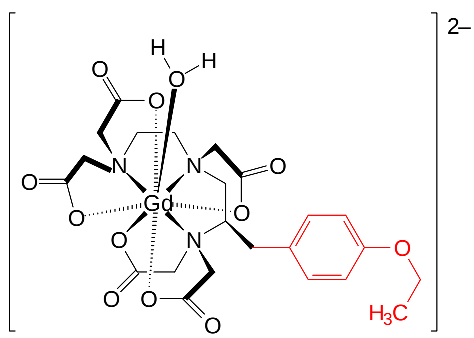


Gadopentetate (Magnevist)

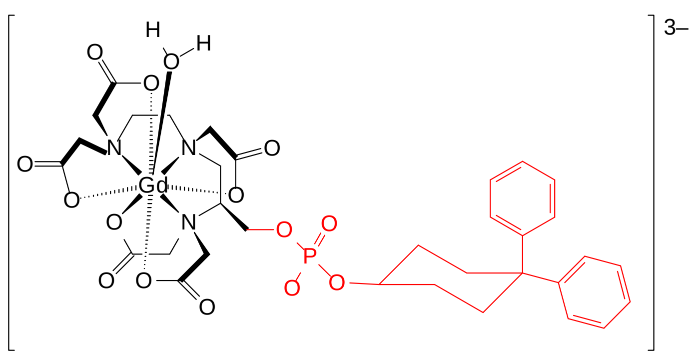
Three other agents have substituents off the DTPA backbone – MultiHance (gadobenate dimeglumine), Eovist (gadoxetate disodium, also known as Primovist), and Ablavar (gadofosveset trisodium, previously known as Vasovist). These modifications alter the biodistribution of the agents and allows for other imaging indications.



Gadobenate (MultiHance)

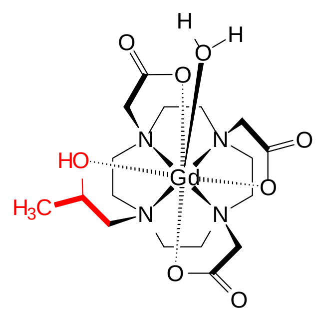


Gadoxetate (Eovist)



Gadofosveset (Ablavar)

Macrocylic agents – Instead of a linear DTPA backbone, the macrocyclic agents possess a 12–membered ring containing four nitrogen ligands. The resulting cage in the macrocyclic group, entrapping the Gd^{3+} ion, is closed, in contrast to the open cages in the linear group. The only drug in this class approved in the US is ProHance (gadoteridol). Two additional macrocyclic agents have been approved elsewhere, Dotarem (gadoterate meglumine) and Gadovist (gadobutrol).



Gadoteridol (Prohance)

These structural differences among macrocyclic and linear groups, and others factors related to structural and electronic considerations do play a role in determining stability. However, details on these roles are not clear, especially when moving from a well–defined in vitro environment to a less well–defined biological environment, relative to normal blood, such as found in renal–impaired disease states with its pool of various ions (metal, phosphate, sulfate), proteins and other substances, and pH. How these differences in environments interact with the structural differences in the gadolinium complexes represents a paucity in our understanding of the roles played by these agents in NSF. With these limitations in view, the following is what we do know.

Stability Trends and Considerations – The thermodynamic stability of metal complexes is expressed as follows, with GdDTPA as an example. Although the reaction represents an equilibrium, it proceeds very strongly toward the right and predominant production of the GdDTPA complex, so the stability constant is very high. For convenience, these numbers are usually referred to as the logarithm, K_{log}, e.g., the log of a stability constant of 1×10^{20} is 20.

$$\mathrm{Gd(III)} + \mathrm{DTPA} \rightleftharpoons \mathrm{Gd(III)DTPA}^{2-}$$

$$\frac{\text{Concentration of product}}{\text{Concentration of reactants}} = \frac{[\mathrm{Gd(III)DTPA}^{2-}]}{[\mathrm{Gd(III)}] \bullet [\mathrm{DTPA}]} = \text{K (therm. stability constant)}$$

Another measure of stability that is more consistent with real–life conditions is the conditional stability constant at pH 7.4. It accounts for the level of protonation of the ligands under physiological conditions, which competes with the ability of secondary amines and acetates to bind to the gadolinium ion. Conditional stability constants are consistently lower than the thermodynamic stability constants.

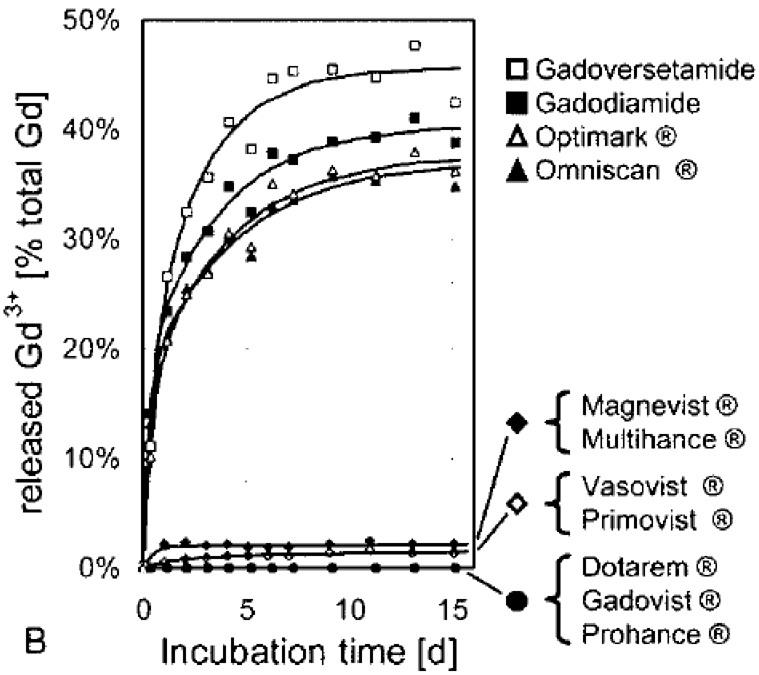
A summary of the stability constants is listed below. Items in gray are not approved in the US.

Tradename	USAN	Log K (thermodynamic)	Log K (conditional, pH 7.4)
Optimark	Gadoversetamide	16.8	15.0
Omniscan	Gadodiamide	16.9	14.9
Vasovist	Gadofosveset	22.1	18.7
Magnevist	Gadopentetate	22.5	18.4
MultiHance	Gadobenate	22.6	18.4
Eovist	Gadoxetate	23.5	18.7
Gadovist	Gadobutrol	21.8	15.5
Prohance	Gadoteridol	23.8	17.2
Dotarem	Gadoterate	25.6	19.3

Ref. Frenzel, T., et al, *Invest. Radiology*, **43**, 817–828 (2008) and references cited within

The stability constants show that the macrocyclic complexes are more stable and the non ionic linear drugs are less stable.

Kinetics of dissociation or transmetallation – The key factor in gadolinium release or transmetallation (exchange of gadolinium for another metal) in vivo relates to what other metals are present that would compete for the chelating ligand. Iron and zinc are known to form very strong complexes with the DTPA class of ligands represented in the known complexes [Fe(III)DTPA, log K = 28.7; ZnDTPA, log K = 18.55; Martell and Smith, *Critical Stability Constants, Volumes 1–4*,(1977)]. In vitro studies in human serum have shown that the linear non–ionics release gadolinium at a measurable rate, which can be accelerated with the addition of phosphate ion, since gadolinium phosphate is exceedingly insoluble and is no longer available in solution to recomplex. (Ref. Frenzel et al). This probably relates to lower energies of activation for the dissociation of the linear non–ionic gadolinium complexes. The complexes based on DTPA release gadolinium slowly but measurably. The macrocyclic complexes did not release measurable amounts of gadolinium, even under the phosphate added experiments. The graph below illustrates the release of gadolinium in human serum with 10 mM phosphate at 37ºC. (Ref. Frenzel et al, ibid)



The gadoversetamide and gadodiamide complexes dissociate faster than the formulated drug products, because there is an excess of ligand or calcium complex in the approved formulations. Most of the less stable gadolinium products are formulated with calcium complexes of the same ligand to help prevent gadolinium dissociation. The use of phosphate ion accelerates the dissociation because any free gadolinium ions will precipitate as the highly insoluble $GdPO_4$.

In summary, the linear nonionic complexes dissociate more rapidly, the linear ionic complexes dissociate more slowly and appear to level off with time, and the macrocyclic complexes remain essentially unchanged. We don't know what effects would be on these trends in moving a given gadolinium complex from the well–defined in–vitro environment in these studies into the biological environment in renal–impaired patients. Data provided in the above graph were obtained in studies using plasma from healthy volunteers, which may not necessarily reflect the composition of plasma or blood from patients with severe renal-impairment. We know that there are likely differences in the composition of blood or blood plasma between normal and renal-impaired patients, including ions (metals, phosphate, sulfate, etc.), proteins and other substances. The absence of an accurate model for use in such studies to appropriately weigh in these factors presents a host of questions on the applicability of current experimental designs to tease out the role of gadolinium complexes in NSF.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Translational Sciences

Date:	November 6, 2009
To:	Chair, Members, and Invited Guests Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees
Through:	Robert Boucher, M.D., M.P.H., Director Division of Pharmacovigilance II, OSE Solomon Iyasu, M.D., M.P.H., Director Amarilys Vega, M.D., Supervisory Medical Officer Laura Governale, Pharm. D., Team Leader Division of Epidemiology, OSE Mark Levenson, Ph.D., Acting Deputy Division Director Aloka Chakravarty, Ph.D., Acting Division Director Division of Biometrics VII, Office of Biostatistics, OTS
From:	James Kaiser, M.D., Medical Officer Division of Pharmacovigilance II, OSE Grace Chai, Pharm.D.,Drug Use Data analyst Julia Ju, Pharm.D., Ph.D., Staff Fellow Division of Epidemiology, OSE Allen Brinker, M.D., Lead Medical Officer Susan Lu, R.Ph., Safety Evaluator Team Leader Division of Pharmacovigilance I, OSE Eiji Ishida, M.S., Staff Fellow Division of Biometrics VI , Office of Biostatistics
Subject:	Gadolinium-Based Contrast Agents and the Risk of Nephrogenic Systemic Fibrosis
Drug Names/License holders/NDAs:	Gadopentetate dimeglumine (Magnevist)/ Bayer / NDAs 019596, 021037 Gadoteridol (Prohance) / Bracco / NDAs 020131, 021489 Gadodiamide (Omniscan) / GE Healthcare / NDAs 020123, 022066 Gadoversetamide (Optimark) / Covidien / NDAs 020937, 020975, 020976 Gadobenate dimeglumine (Multihance) / Bracco / NDAs 021357, 021358
OSE RCM #:	2009-1101

(b) (4)

CONTRIBUTORS

This document represents the work of analysts within the Office of Surveillance and Epidemiology (OSE) and the Office of Translational Sciences (OTS).

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- OSE Scientific Lead: James Kaiser, M.D., Medical Officer, Division of Pharmacovigilance II*

The following is a list of the analysts and their work:

For OSE –

- Grace Chai, Pharm. D. (Division of Epidemiology, OSE): Drug use data assessment
- Allen Brinker, M.D. and Susan Lu, R.Ph. (Division of Pharmacovigilance I,* OSE): Postmarketing adverse event assessment
- Julia Ju, Pharm. D., Ph.D.(Division of Epidemiology, OSE): Literature review

For OTS –

- Eiji Ishida, M.S. (Division of Biometrics VI**, Office of Biostatistics, OTS): Disproportionality assessment

The analyses were compiled by James Kaiser, M.D.

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- Robert Boucher, M.D., M.P.H.
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CONTENTS

1 EXECUTIVE SUMMARY

The association of gadolinium-based contrast agents (GBCAs) with nephrogenic systemic fibrosis (NSF) was first made in the literature in 2006. Over the ensuing years both FDA and EMEA have addressed this issue. Currently, FDA supports class labeling for risk, while EMEA warns of risk differentially across agents, contraindicating selected products in specific clinical circumstances. The current review summarizes several lines of evidence regarding the possibility of differences in risk: sales data from 2005 to the present, postmarketing adverse event reports, physicochemical data, and the literature.

Based on sales volume in conjunction with the numbers of single-agent cases, the risk signals of Omniscan, Magnevist, and Optimark have been greatest among the GBCAs considered in this review. Among single-agent cases, there have been no domestic reports and one nondomestic report associated with Prohance, and one domestic report of NSF in association with Multihance.

The literature on the association of NSF and GBCAs is inadequate to determine the differential risk of the various agents.

Laboratory data suggest that the structure of the gadolinium-chelator complex (i.e., linear as opposed to macrocyclic) likely plays an important role in the pathogenesis of NSF.

The different lines of evidence cited in this review all have limitations, some of which are substantial. These limitations are described in the review. However, based on the preponderance of the evidence in this review, it is OSE's judgment that GBCAs are associated with varying risk of NSF. The highest risk is associated with Omniscan, Magnevist, and Optimark. The lowest risk is associated with Prohance and Multihance. The other domestically-approved agents are not considered in this review as they do not yet have significant market exposure.

The magnitude and nature of NSF risk does not warrant market removal for any specific GBCAs at this time.

We note that the field of NSF research is rapidly evolving. While this document represents the current evidence-based opinion of OSE, it is plausible that additional, relevant information may become available to OSE prior to the Advisory Committee meeting that warrants presentation to the Committee.

2 RECOMENDATIONS

The OSE joint recommendation is:

> Differential labeling of GBCAs for use in certain populations reflecting varying risk across products

OSE will work with the Division of Medical Imaging and Hematology Products and manufacturers to produce labeling that appropriately reflects our current understanding of the risk of NSF with specific GBCAs.

3 BACKGROUND

3.1 INTRODUCTION

3.1.1 Nephrogenic systemic fibrosis (NSF)

NSF is a rare, debilitating and sometimes fatal fibrosing condition of persons with renal failure. The first published cases occurred in 1997[1,2]; it was first called nephrogenic fibrosing dermopathy, as it was originally thought only to affect the skin. In NSF connective tissue fibrosis develops about the arms, legs, and trunk that may limit mobility. It is now known that fibrotic lesions may also occur in deeper structures, such as muscle, fascia, lungs, and heart. The disorder occurs without predilection for race, age, or sex. There is no accepted treatment for NSF.

3.1.2 Renal dysfunction

Chronic kidney disease (CKD) is defined as either kidney damage or a GFR of less than 60 mL/min/1.73m^2 for more than 3 months. Table 1 shows the five stages of CKD and corresponding glomerular filtration rate (GFR) based on the CKD classification system of the National Kidney Foundation[3]. This document will refer to this classification scheme.

Table 1. Stages of chronic kidney disease (CKD)

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or on dialysis*

* Dialysis includes hemodialysis (HD) and peritoneal dialysis (PD)

3.1.3 Gadolinium-based contrast agents (GBCAs)

Grobner et al.[4] first described an association between gadolinium-based contrast agents (GBCAs) and NSF. GBCAs are used as adjuncts to magnetic resonance imaging to improve visualization of internal structures. Table 1 shows all approved GBCAs considered in this review. Vasovist (gadofosveset trisodium, now known as Ablavar) and Eovist (gadoxetate disodium) were both approved in 2008 and are not considered in this review.

This review will refer to the GBCAs by their proprietary names.

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1 Cowper SE et al. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet 2000; 356: 1000-1001.
2 MMWR Morb Mortal Wkly Rep. 2002 Jan 18;51:25-6
3 The chronic kidney disease classification system of the National Kidney Foundation Kidney Disease Outcome Quality Initiative. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39 (2 suppl 1): S1-S266.
4 Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis. Nephrol Dial Transplant. 2006; 21:1104-8

Table 2. Approved gadolinium-based contrast agents considered in this review

	Gadolinium-Based Contrast Agent Tradename / Company				
	Magnevist/ Bayer	**Prohance/ Bracco**	**Omniscan/ GE**	**Optimark/ Covidien**	**Multihance/ Bracco**
Active moiety	gadopentetate dimeglumine	Gadoteridol	gadodiamide	gadoversetamide	gadobenate dimeglumine
Year approved in US	1988	1992	1993	1999	2004
Indication (body area imaged	Adults and children ≥2 years old: CNS and associated tissues, head and neck, body excluding heart	Adults and children ≥2 years old: CNS and associated tissues Adults: head and neck	Adults and children ≥ 2 years old: Brain, spine, associated tissues; intrathoracic, intra-abdominal, pelvic, retroperitoneal space	Brain, spine, associated tissues; liver	Brain, spine, associated tissues
Approved adult dose (mmol/kg)	0.1	CNS: 0.1; 0.2 may be given ≤ 30' later Extracranial/extraspinal: 0.1	CNS: 0.1; 0.2 may be given 20' later Kidney: 0.05 Other: 0.01	0.1	0.1
Approved pediatric dose (mmol/kg)	0.1	CNS: 0.1 Extracranial/extraspinal: Not applicable	CNS: 0.1 Kidney: 0.05 Other: 0.01	Not applicable	Not applicable

3.1.4 Pathogenesis of NSF

Free gadolinium is a highly toxic rare earth metal. Gadolinium has been found in skin and soft tissue[5] and bone[6] of patients with NSF. Due to free gadolinium's toxicity the GBCAs are formulated to isolate it within a molecule, a chelator, which binds the ion. The strength of binding is determined by the structure of the chelator, which may be linear or cyclic (forming a "cage" around the gadolinium ion), and by ionicity. When determined in nonphysiologic solutions, the stability of the macrocyclic agents is orders of magnitude more than that of linear agents. In one study gadolinium agents incubated with human serum at body temperature *in vitro* over 15 days performed as expected[7]. Linear structures released gadolinium much more readily and in far greater amounts than macrocyclic ones and linear nonionic agents released more gadolinium than linear ionic ones. Of the 5 US-approved GBCAs considered in this review, 4 (Magnevist, Omniscan, Optimark, Multihance) have gadolinium bound to a linear chelator and 1 (Prohance) to a macrocyclic chelator (refer to Table 3).

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[5] High, WA et al. Gadolinium is quantifiable within the tissue of patients with nephrogenic systemic fibrosis. J Am Acad Dermatol 2007; 56:710-2.

[6] White GW et al. Comparison of Gd(DTPA-BMA) (Omniscan) Versus Gd(HP-DO3A) (ProHance) Relative to Gadolinium Retention in Human Bone Tissue by Inductively Coupled Plasma Mass Spectroscopy. Invest Radiol. 2006 Mar;41(3):272-8.

[7] Frenzel T et al. Stability of Gadolinium-Based Magnetic Resonance Imaging Contrast Agents in Human Serum at 37°C. Invest Radiol. 2008 Dec;43(12):817-28.

Table 3. Structure, physiochemical properties, route of elimination, and doses of the GBCAs

Trade name	Structure of chelator	Ionicity of complex	Primary route of elimination
Magnevist	Linear	ionic	renal
Prohance	Macrocyclic	nonionic	renal
Omniscan	Linear	nonionic	renal
Optimark	Linear	nonionic	renal
Multihance	Linear	ionic	renal (97%); biliary (3%)

The role of free versus chelated gadolinium in NSF remains an open question. Some *in vitro* work suggests that chelated gadolinium may contribute to a fibrotic response[8,9]. There are also data showing that more gadolinium was found in skin of rats exposed to linear GBCAs than to macrocyclic ones [10]; however, the addition of excess chelator to linear, ionic contrast formulations given intravenously to rats lessened the incidence of fibrosis/sclerosis and increased cellularity in the skin[11], which suggests a role for free gadolinium in NSF pathogenesis.

The release of free gadolinium from the chelated molecule may also be promoted by a process called "transmetallation." Some metal ions (for example, iron) bind to GBCA chelators more avidly than gadolinium. When competing ions are present they may exchange places with gadolinium; due to the greater binding avidity favoring the non-gadolinium ion the free gadolinium is less likely to re-bind to its original site. Additionally, some proteins and inorganic ions such as phosphate bind gadolinium. Transmetallation may occur *in vivo*[12].

Elimination of gadolinium-chelator complexes is slower in renal failure[13,14], as the primary route of elimination from the body is through the kidney. This results in greater systemic exposure. It is also reasonable to expect that dose may play a role. Other factors, such as elevated serum phosphate and calcium[15], tissue injury[16]; and high-dose erythropoietin[17], are proposed as contributing to the pathogenesis of NSF.

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[8] Varani J et al. Effects of Gadolinium-Based Magnetic Resonance Imaging Contrast Agents on Human Skin in Organ Culture and Human Skin Fibroblasts. Invest Radiol. 2009 Feb;44(2):74-81

[9] Edward M et al. Gadodiamide contrast agent 'activates' fibroblasts: a possible cause of nephrogenic systemic fibrosis. J Pathol. 2008 Apr;214(5):584-93

[10] Pietsch H et al. Long-term retention of gadolinium in the skin of rodents following the administration of gadolinium-based contrast agents. Eur Radiol. 2009 Jun;19(6):1417-24

[11] Sieber MA et al. Gadolinium-Based Contrast Agents and Their Potential Role in the Pathogenesis of Nephrogenic Systemic Fibrosis: The Role of Excess Ligand J Magn Reson Imaging 2008;27:955–962.

[12] Thakral C and Abraham JL. Gadolinium-Induced Nephrogenic Systemic Fibrosis Is Associated with Insoluble Gd Deposits in Tissues: In Vivo Transmetallation Confirmed by Microanalysis. J Cutan Pathol. 2009; 36(12): 1244-54. Also published on the internet on July 7, 2009.

[13] Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. Acad Radiol 1998;5:491–502.

[14] Tombach B et al. Pharmacokinetics of 1M gadobutrol in patients with chronic renal failure. Invest Radiol. 2000 Jan;35(1):35-40

[15] Marckman P et al. Case-control study of gadodiamide-related nephrogenic systemic fibrosis. Nephrol Dial Transplant. 2007 Nov;22(11):3174-8. Epub 2007 May 4

[16] Sadowski, EA, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. Radiology 2007; 243:148

[17] Swaminathan S et al. Nephrogenic fibrosing dermopathy and high-dose erythropoietin therapy. Ann Intern Med. 2006 Aug 1;145(3):234-5

3.2 REGULATORY HISTORY

3.2.1 FDA and EMEA responses to emerging safety data concerning GBCAs and NSF

FDA

Highlights of FDA actions with respect to the safety issue of GBCAs with NSF are listed below:

- On June 8, 2006 FDA issued a Public Health Advisory, an Information for Healthcare Professionals, and Question and Answers [18,19,20]. These were based on an analysis of 25 cases of NSF in Danish and Austrian patients with renal failure who had undergone Magnetic Resonance Angiography (MRA) with Omniscan. These notices, which contained guidelines to reduce the risk of NSF, did not distinguish a potential risk of NSF among the GBCAs approved at the time.
- On December 22, 2006 FDA issued an updated Public Health Advisory, Information for Healthcare Practitioners, and Question and Answers based on reports of NSF from June 2006 to December 21, 2006 in 90 patients [21,22,23] These patients, which included the 25 who had been previously reported, had received a GBCA for either MRI or MRA. All patients had glomerular filtration rates below 60 ml/min/1.73 m^2. FDA did not distinguish a difference in risk among the GBCAs, stating "Though NSF/NFD has been reported following administration of three of the FDA approved gadolinium-based contrast agents (Magnevist, Omniscan, and Optimark), FDA believes that there is a potential for NSF/NFD to occur in patients at risk following administration of any of the approved gadolinium-based contrast agents."
- On May 22, 2007 FDA requested a boxed warning about the risk of NSF from the license holders of each approved GBCA, and on May 23 of that year issued an updated Information for Healthcare Professionals stating this fact [24,25,26]. FDA noted that "Omniscan was the most commonly reported agent, when a specific agent was identified, followed by Magnevist and Optimark. NSF also has developed after the sequential administration of Omniscan and Multihance and Omniscan and Prohance. Because reports incompletely describe exposure to gadolinium-based contrast agents, it is not possible to know if the extent of risks for developing NSF is the same for all agents."
- The May 22, 2007 FDA letter requested from the license holders of the approved GBCAs a proposal for a post-marketing commitment to conduct a study to "collect clinical data

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[18] Information for Healthcare Professionals - Gadolinium-Containing Contrast Agents for Magnetic Resonance Imaging (MRI) (marketed as Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance) 6/8/06

[19] Public Health Advisory: Gadolinium-containing Contrast Agents for Magnetic Resonance Imaging (MRI). 6/8/2006

[20] Questions and Answers on Gadolinium-Containing Contrast Agents 6/8/2006

[21] Information for Healthcare Professionals Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging Scans (marketed as Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance) 12/2006

[22] Public Health Advisory: Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy 12/22/2006

[23] Questions and Answers on Gadolinium-Based Contrast Agents 12/22/06

[24] Information for Healthcare Professionals Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging (marketed as Magnevist, MultiHance, Omniscan, OptiMARK, ProHance) FDA ALERT [6/2006, updated 12/2006 and 5/23/2007]

[25] FDA Requests Boxed Warning for Contrast Agents Used to Improve MRI Images 5/23/2007

[26] Questions and Answers on Gadolinium-Based Contrast Agents (last updated September 1, 2009)

sufficient to assess the magnitude of risk for the development of NSF with your product among patients with moderate (GFR < 60 mL/min/1.73m^2) to more severe renal insufficiency."

EMEA

Unlike FDA, the European Medicines Agency (EMEA) has stratified risk among the GBCAs. In February 2007 the EMEA issued a Direct Healthcare Professional Communication (DHPC) stating that 1) Omniscan should not be used in patients with severe renal impairment (glomerular filtration rate <30 ml/min/1.73 m^2) or who have had or are awaiting liver transplantation and 2) careful consideration should be given to the use of other GBCAs in patients with severe renal impairment. A June 2007 DHCP added advice to consider carefully the use of Omniscan in patients with moderate renal dysfunction (glomerular filtration rate 30-59 ml/min/1.73 m^2) or in children up to the age of 1. The June 2007 DHCP added similar contraindications and cautions for the use of Magnevist. Fewer strictures and cautions were administered for the use of the other GBCAs; the DHCP stated that careful consideration should be exercised for their use in patients with severe renal impairment.

3.3 PRODUCT LABELING

GBCAs have a common boxed warning in product labeling that states, regarding NSF:

- Gadolinium-based contrast agents (GBCAs) increase risk of NSF in patients with:
  - acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2), or
  - acute renal insufficiency of any severity due to hepato-renal syndrome or in perioperative liver transplantation period.
- In these patients, avoid use of GBCAs unless diagnostic information is essential and not available with non-contrast enhanced MRI.
- NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs.

Labeling also cautions against the risk of NSF in the Warnings and Precautions section (Appendix 1). The Postmarketing Experience section names NSF as an adverse reaction.

4 INTENT AND SCOPE OF REVIEW

The Office of Surveillance and Epidemiology and the Office of Translational Sciences conducted analyses of information pertaining to the possibility of differences in the risk of NSF after exposure to GBCAs that were available at the time of recent FDA actions (see above). These agents are Magnevist, and Prohance, Omniscan, Optimark, and Multihance, The Office examined three types of data regarding the risk of development of NSF after gadolinium exposure.

- Sales and use data
- Cases submitted to FDA's Adverse Event Reporting System (AERS). FDA's Division of Drug Risk Evaluation had reviewed the AERS data base previously.[27,28]
- Published literature

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[27] Memorandum dated May 10, 2007. From Allen Brinker, Susan Lu, Kate Gelperin to Rafel (Dwaine) Rieves. Nephrogenic systemic fibrosis in association with gadolinium-based contrast agents.

[28] Memorandum dated June 20, 2008. From Allen Brinker to Rafel (Dwaine) Rieves. Review of a proposed prospective, open-label non-controlled cohort study submitted for gadoxetic acid for Nephrogenic Systemic Fibrosis (NSF) in comparison to similar protocols submitted for the 5 currently marketed gadolinium-based contrast agents (GBCAs) and other issues relevant for GBCAs and NSF.

This document compiles these analyses and presents the judgment of the Office of Surveillance regarding this issue.

5 DRUG USE REVIEW

5.1 MATERIALS AND METHODS

Proprietary drug use databases licensed by FDA were analyzed. These databases are the IMS Health, IMS National Sales Perspectives™ data from which the primary settings of use were determined based on sales distribution, and the Premier RxMarket Advisor™ from which inpatient hospital utilization were determined.

5.2 RESULTS

5.2.1 GBCA sales

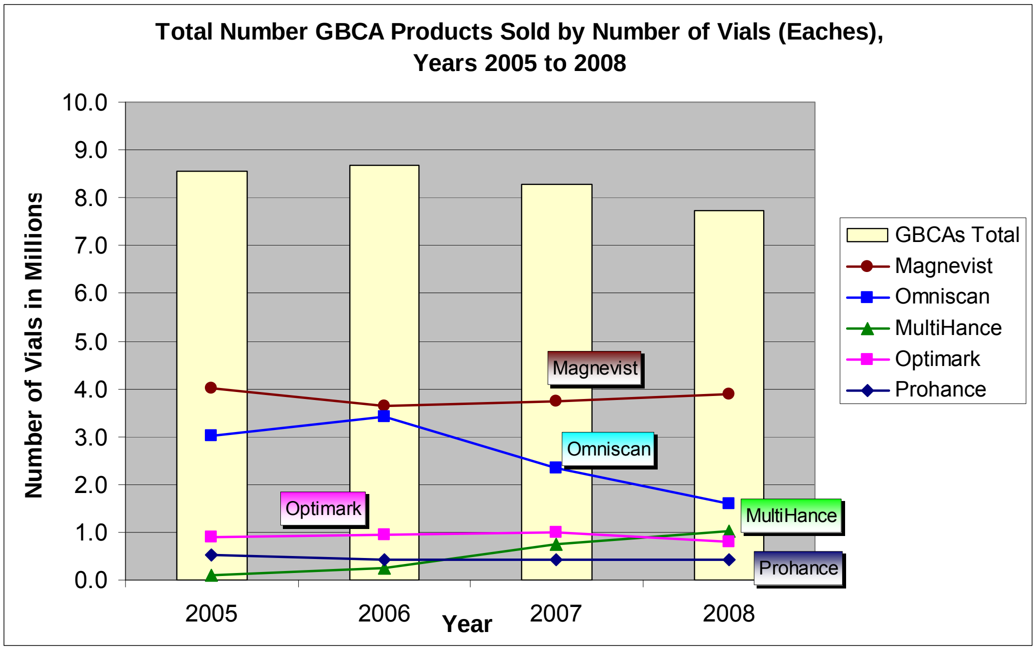
Limitations on interpretation of sales data from IMS

IMS Health, IMS National Sales Perspectives™ data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution (Appendix 2.1). The amount of product purchased is a reasonable surrogate for use, as facilities tend to purchase drugs in quantities reflective of actual patient use.

Vials of GBCAs sold by product

Figure 1 shows that in year 2008, the majority of the sales of GBCA products were of the product brand, Magnevist at around 50% of the market share in year 2008. Magnevist has consistently been the top selling GBCA product over the examined time period of year 2005 to year to date June 2009. Omniscan was second in sales but has decreased from almost 40% of the market share in year 2006 to about 20% in year 2008. Multihance has shown an increase in sales from ~1% of the market share in year 2005 to ~13% of the market share in year 2008. The other GBCA products have either remained relatively consistent in sales over the examined time period

Figure 1. Vials of GBCAs sold from 2005 through 2008

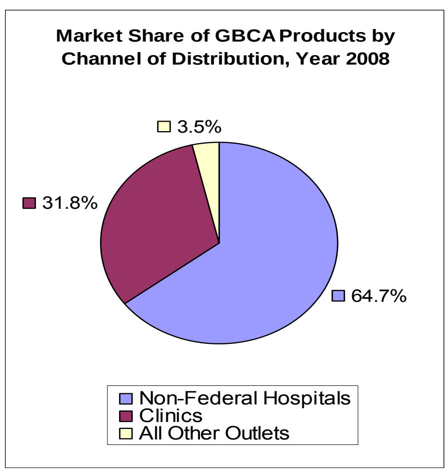


Source: IMS Health, IMS National Sales Perspectives™, Year 2005-2009, extracted 8-09.

<u>Settings for sales of GBCAs as a whole</u>

During the period of analysis, year 2005 through Q2 year 2009, the proportions of sales accounted for by the various settings did not vary markedly. In year 2008, non-federal hospitals accounted for the majority of GBCA sales (~65% of vials sold) followed by clinic settings (~32% of vials sold, Figure 2). Other settings, including federal hospitals, accounted for ~3% of market share.

Figure 2. Settings of Sales of GBCAs in 2008



IMS Health, IMS National Sales Perspectives™, Year 2005-2009, extracted 8-09. File: 0908gado.xls

<u>Estimated number of milliliters sold</u>

We also obtained the estimated number of milliliters (ml) of GBCA products sold over the study period to ascertain the number of individual doses sold during this time period. Approximately 151 million ml of GBCAs were sold in year 2008, down from approximately 158 million ml in year 2005 (Appendix 3,Table 16). Assuming that the standard dose administered for a gadolinium agent is 14 ml (based on standard dosing at 0.2 ml/kg and 70 kg as an average human weight), we estimate that approximately 11.3 million doses were sold in year 2005 compared to 10.8 million doses in year 2008.

5.2.2 GBCA inpatient use

Limitations on interpretation of use data from Premier

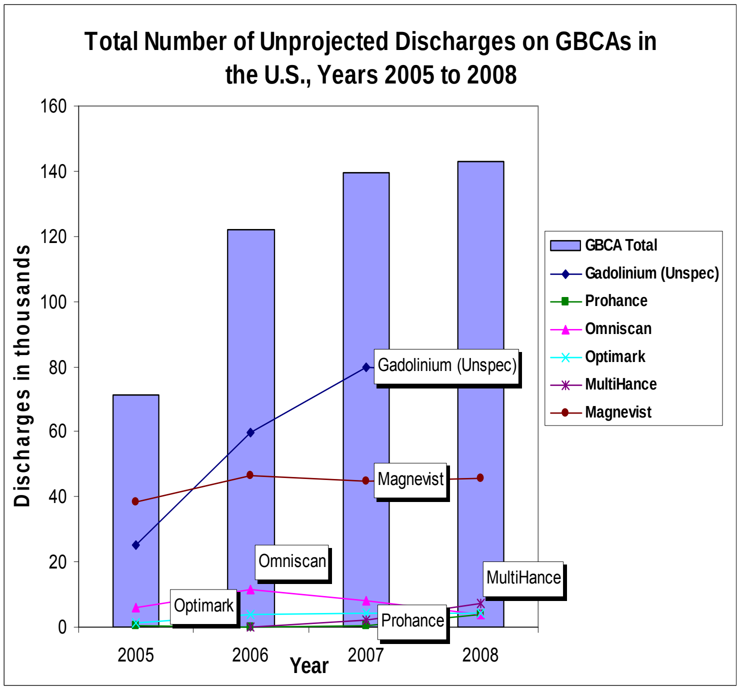
The Premier Healthcare Informatics, RxMarket Advisor™ data are derived from hospital discharge billing. These inpatient data are heavily influenced by the method of billing or recording of GBCA products. Since 2006, over half of all inpatient discharge billings for GBCA products were reported under the generic code "Gadolinium (Unspecified)," making estimates of individual product use problematic. However, the available specific product data are consistent with sales data. This review shows analysis of all gadolinium use (i.e., where brand was specified and where it was unspecified) by raw data and projected numbers produced by Premier. The latter reflect estimates of national inpatient utilization.

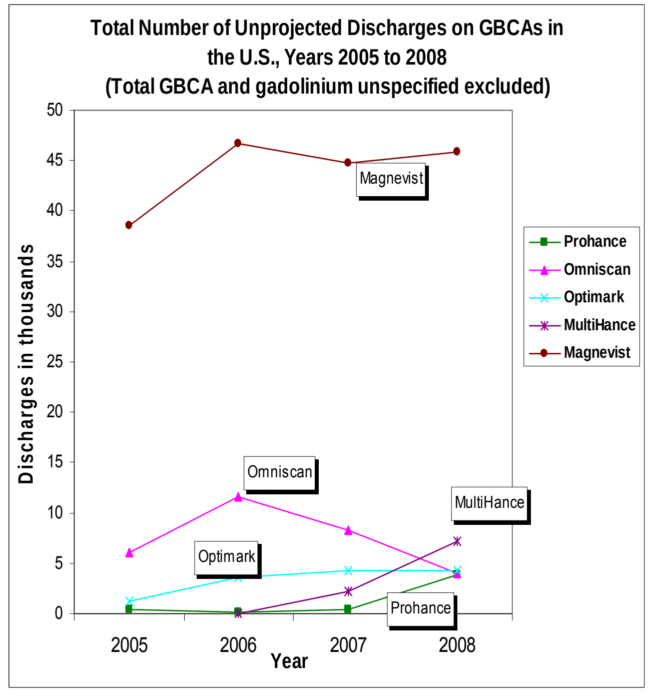
From January 2005 to May 2009, approximately 500,000 discharges (Appendix 3,Table 17 and 490,000 unique patients (Appendix 3, Table 18) were billed for a GBCA. Premier projects that this would be an estimated 3.6 million discharges and 3.3 million unique patients billed for a GBCA nationally (Appendix 3: Tables 3 and 4).

In contrast to sales distribution data, the number of hospital discharges (Appendix 4,Table 17) and patients with a billing for GBCA product (Appendix 4, Table 18) within the Premier network of hospitals increased over the time period. A subset of hospitals in the Premier database reported GBCA use by specific product. The number of hospitals reporting GBCA use by specific product increased from 101 in 2005 to 182 in 2008 (142, year-to-date in 2009, Appendix 5). Since these nationally projected estimates made by Premier are not based on those 101-182 hospitals that report specifically for individual gadolinium products, we included the unprojected discharge data to show trends for those product-specific hospitals alone.

Similar to the sales data, among the cases where the GBCA was specified, the majority of the discharges (Appendix 4, Table 17) and patients (Appendix 4,Table 18) were associated with Magnevist. Among cases where the GBCA was specified, there was a decrease in the number of discharges and patients associated with Omniscan use beginning in 2006. However, there were increases in the number of discharges and patients associated with both Multihance and Prohance from 2005 to 2008. Optimark discharge and use per patient were relatively constant for the examined time period.

Figure 3. Unprojected discharges associated with different GBCAs (and unspecified GBCAs)





Premier Healthcare Informatics, RxMarket Advisor™, data extracted 8-09.

5.2.3 Summary of drug use data

Utilization (as opposed to sales) of specific GBCA products was difficult to assess due to unspecified product reporting in the inpatient setting. Analysis of projected sales data is a good surrogate for estimating national use of GBCA products. The analysis reveals that:

- Approximately 7.7 million vials of GBCA products were sold in year 2008, down from 8.5 million vials in year 2005.
- Non-federal hospital settings accounted for the majority of GBCA sales, followed by clinic settings as the primary channel of distribution throughout the examined time period.
- The majority of the sales of GBCA products were of Magnevist at around 50% of the market share in year 2008. Omniscan was second in sales but has decreased from almost 40% of the market share in year 2006 to about 20% in year 2008. Multihance has shown an increase in sales while the other GBCA products have either remained relatively consistent in sales over the examined time period.

Inpatient data for drug usage of GBCA products was also analyzed but contained some limitations.

- From January 2005 to May 2009, a total number of approximately 3.6 million projected discharges and approximately 3.3 million projected unique patients were billed for a GBCA.
- Inpatient utilization data from Premier for gadolinium products as a whole reflected the trends of the sales data of the GBCA products. Unfortunately, a large portion of the data has been reported as “gadolinium” or “unspecified” GBCA. Data excluding those hospitals that report “gadolinium” or “unspecified” GBCA were more reflective of sales data trends. The majority of use, from those product-specific reporting hospitals, was for Magnevist while use

for Omniscan decreased beginning in 2007 and has remained well below that for Magnevist following a FDA drug safety communication in May 2007.

6 AERS REVIEW

6.1 MATERIALS AND METHODS

Description of the AERS database

FDA receives reports of adverse events through the MedWatch system. Reports come from a variety of sources, including manufacturers, patients, healthcare providers, relatives or other observers, and lawyers, for example. These reports are entered into a data base called AERS, the Adverse Event Reporting System. Adverse events are coded into standardized international medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events are commonly analyzed by the "preferred term" or "PT" by which the event has been encoded. Other information such as patient age, sex, concomitant medications and others, may be included in the report. The quantity and quality of data in reports is variable.

Limitations of these AERS data

Spontaneous reporting data are generally not useful for determining incidence rates, due to uncertainties in factors that influence reporting of adverse events. Some reports were submitted to AERS within batches from selected institutions, which imposes an additional limitation. Batch reporting suggests that some reporting was not spontaneous and these cases are not independent of each other. The calculation of rates from AERS data depends upon an assumption that reports occur spontaneously, and are not stimulated. To some degree, differential risk assessment is also complicated by uncertainties in the quantities of GBCA given, and possibly by different definitions of NSF by manufacturers (for manufacturer-submitted reports). Nevertheless, certain observations may be made regarding the numbers of reports, as described below.

Description of the AERS search for domestic NSF cases associated with GBCAs

A search of the AERS database was conducted on September 3, 2009 to identify domestic reports of nephrogenic systemic fibrosis for each of the marketed gadolinium contrast agents. The search strategy included the drugs Omniscan® (gadodiamide), Magnevist® (gadopentetate dimeglumine), Optimark® (gadoversetamide), Prohance® (gadoteridol), Multihance® (gadobenate dimeglumine) and the MedDRA preferred term (PT) "nephrogenic systemic fibrosis." FDA receipt dates were not restricted and included all U.S. reports of NSF from U.S. marketing introduction of each product.

Description of the disproportionality analysis for all cases of NSF associated with GBCAs

The objective of the disproportionality analysis was to determine whether NSF was associated with one GBCA more than the others, using adverse event cases in which at least one of the gadolinium class of contrast agent drugs was listed as the primary suspect agent. The numbers of cases of NSF and all other adverse events associated with each GBCA are analyzed simultaneously, to determine any notable differences among the products in the relative numbers of reports of a given event. It is conceivable that a product with a notably better safety record of non-NSF cases would yield a higher relative risk of NSF. However, it is relatively unlikely that this would be the case in a restricted class of drugs like the GBCAs.

6.2 RESULTS

6.2.1 AERS case review

6.2.1.1 Crude numbers of reports in association with different GBCAs

Crude report counts obtained for the AERS database are shown in Table 4. It is important to note that the crude data may contain some duplicate reports, as not all reports were subject to detailed review. It is also important to note that these data are not adjusted for amount of exposure to the drugs. Table 4 shows report total report count by agent and also include reports listing only a single brand. Notwithstanding the general limitations of AERS reports, OSE considers the single-agent reports more interpretable than those listing multiple agents. As noted in the subtext for the table, although there are no domestic single-agent NSF reports for Prohance, the AERS database does contain one foreign report of NSF in association with Prohance only.

Although the recently-approved (2008) GBCAs Ablavar (formerly Vasovist) and Eovist are not considered in this document, it is worth noting that there are no domestic MedWatch reports for these agents.

Table 4. Crude numbers of domestic reports of NSF for each gadolinium contrast agent*

Product	Year of FDA Approval	Domestic NSF Reports in AERS	Domestic Single-agent NSF Reports in AERS**
Omniscan	1993	929	382
Magnevist	1988	654	195
Optimark	1999	427	35
Prohance	1992	325	0***
Multihance	2004	335	1

*Crude counts are generated from search terms, and are not screened for duplicated submissions or submissions with unclear relevance. They do not take into account relative use of the products.
** Reports listing a single gadolinium agent. Reports with more than one gadolinium agent or unspecified gadolinium agents were mentioned were excluded. OSE considers these reports more interpretable than reports listing multiple agents.
*** Although there are no domestic single-agent NSF reports for Prohance, AERS contains one foreign report of NSF in which a patient received only Prohance.

6.2.1.2 Cumulative reports by receipt date at FDA and by event date

Many reports in the series list numerous GBCAs in the report, i.e., they include many agents as primary suspects in the development of NSF. While the sum of report counts for all GBCAs by agent is 2,670 (Table 4, third column), the sum of reports for all GBCAs by the class is only 1,128. The cumulative frequency of reporting by the class by receipt date to the Agency is shown in Figure 4.

Figure 4. Cumulative domestic MedWatch reports of NSF in association with GBCAs as a class by initial FDA receipt date (n=1128) and for the subset of all reports with an event date (n=666) through September 3, 2009

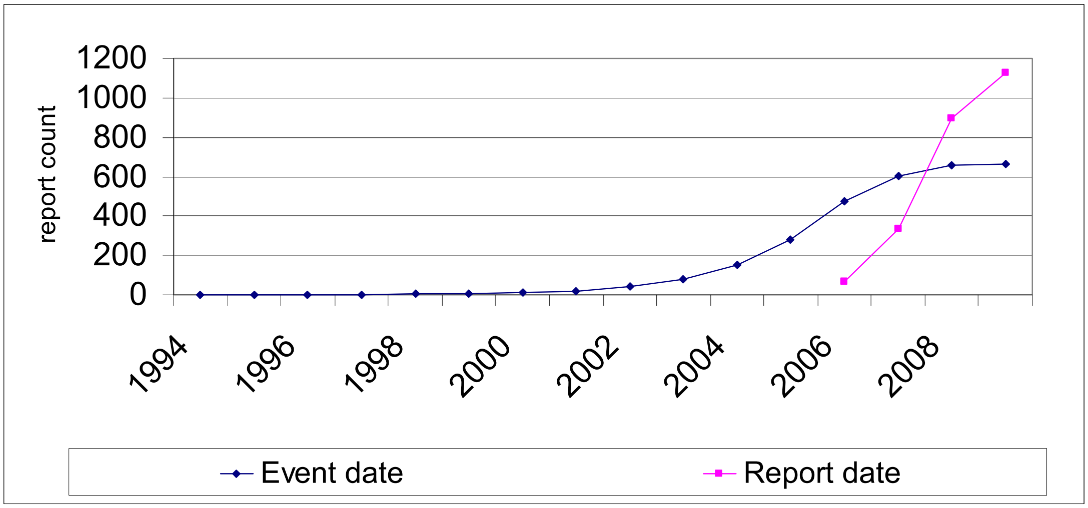


Figure 4 also shows the cumulative frequency of reports in which the event date is included. "Event date" may represent different dates, for example, first exposure to a GBCA or receipt of a diagnosis of NSF. The average "lag" in reporting from these data, that is, the difference between report date and event date, is 2.4 years. Very few of the reports received by the FDA since January 1, 2008, describe cases in which administration of a GBCA was on or after 2006, when FDA its first public advisory on the issue of NSF with GBCAs (see "Analysis of recent reports" below).

6.2.1.3 Examination for reports with GFR specified as ≥30 ml/min/m^2

The narratives of NSF reports were searched to identify reports containing information where the text "GFR" or "glomerular filtration rate" indicated moderate renal dysfunction or better (i.e., GFR≥30 ml/min/m^2). Six reports were identified, of which 2 involved the administration of more than one type of GBCA. Four reports of single-agent gadolinium exposure (Omniscan [n=1], Magnevist [n=3]) in patients with GFR≥30 ml/min/m^2 were identified:

- A 55 year-old female with Stage 3 chronic renal failure (eGFRs ranging from 30-40 ml/min/m^2 at time of procedure) had two contrast procedures within a 24 hour time period with Omniscan (2x30 ml doses); the patient died 10 months following NSF diagnosis. The cause of death was underlying disease in which a contributory role of NSF was proposed.
- A 59 year-old patient with apparently normal renal function (reported as eGFR=92) received Magnevist for MRI and MRA. However, the eGFR measurement was performed 3 months before the MRI/MRA procedures.
- A 63 year-old female with moderate renal impairment (eGFR=55) developed biopsy-proven NSF subsequent to receiving Magnevist for an MRI.
- A 92 year-old male with chronic kidney disease (GFR 43ml/min) developed NSF after MRI with Magnevist.

In only one of these cases was a GFR ≥30 ml/min/m^2 reported at the time of administration of a GBCA. Full clinical narratives of these 6 cases are presented for completeness (Appendix 6).

6.2.2 Disproportionality analysis

Limitations of the disproportionality analysis
The signal detection measures discussed here are intended for research hypothesis generation and are not designed to obtain risk estimates or perform product-related statistical inferences. They provide information on the spontaneous reporting of a safety related event of interest in a descriptive manner and, as such, may suggest potential drug risks reflected in the reporting to the AERS database if there is a signal detected.

Assumptions underlying the analysis (class analysis)
Signal detection may be performed on all drugs or on a selection of drugs. The current analysis is performed only within the same, i.e., gadolinium, class of contrast agent drugs rather than the AERS database for all the drugs, to provide more precise comparisons. This is based on a conjecture that a drug adverse reaction is generally more similar within the same class of drugs than in the entire set of drugs.

Results
Table 5 shows measures of relative reporting of NSF for each product in comparison to the other products. These measures are the "proportional reporting ratio" (PRR) and the "relative reporting ratio" (RRR), defined as follows:

- Proportional Reporting Ratio (PRR): The PRR is the proportion of voluntary reports for a given drug that are linked to a specific adverse outcome, e.g.., NSF, divided by the corresponding proportion for the other drugs under consideration. A higher value of PRR for one GBCA indicates higher reporting, conceptualized as a higher signal for NSF signal, compared to the other GBCAs. The PRR is not a measure of absolute drug risk, but rather a measure of disproportionality of the frequency of reports compared to other drugs (in this case, drugs in the same class).
- Relative Reporting Ratio (RRR): The Relative Reporting Ratio (RRR) measures a relative reporting rate in comparison with the overall reporting occurrence of all adverse event reports for the comparison drugs. In this case it is defined as the observed number of NSF reports for the GBCA of interest divided by expected number of reports. The expected number of reports is (the sum of NSF and non-NSF reports on the drug of interest) times (the proportion of the total number of NSF reports on the drug of interest against the total number of the reports on both the groups). Thus the expected number of reports is computed under the assumption that no difference between one gadolinium drug and all the other gadolinium drugs exists. The expected number of reports is the number of reports on the drug of interest that would occur if the report occurred at the same rate as the overall occurrence of the report for all the gadolinium drugs. Therefore, a RRR measures a relative reporting rate in comparison with the overall reporting occurrence. This definition is equivalent to the proportion of an NSF report on the drug of interest divided by the overall proportion based on all the drugs.

Table 5. Data Mining analysis: Proportional Reporting Ratio and Relative Reporting Ratio for domestic cases of NSF among GBCAs listed as a single agent

Drugs of interest	Observed Count	Proportional Reporting Ratio (PRR)	Relative Reporting Ratio (RRR)
Magnevist	162	0.283	0.461
Prohance	0	0	0
Omniscan	457	21.609	7.186
Optimark	32	5.695	5.465
Multihance	2	0.025	0.028

1) The event of interest is defined by the preferred term "nephrogenic systemic fibrosis" in MedDRA version 12.0.
2) If no nephrogenic systemic fibrosis cases were present, PRR and RRR were not calculated for the drug.
3) The numbers of observed counts differ in detail, but not magnitude, from the counts shown in Table 4 due to differences in the algorithms used to extract the cases from the AERS data base.

According to this analysis the PRR and RRR of Omniscan and Optimark are notably higher than those of the other GBCAs. It should be noted that the data mining analysis is a measure of reporting of the case type of interest as compared to other reports in the data base, and is not directly comparable to the rough measures of risk from direct reports and sales.

6.3 SUMMARY OF AERS REVIEW

As stated previously, these AERS data are subject to various limitations. Even with these limitations, however, it is noteworthy that the great majority of reports are associated with Omniscan and Magnevist, and that there are no domestic reports of NSF after administration of Prohance only (and only one foreign Prohance/NSF report). Among cases in which event dates were reported, the frequency of cases occurring after 2006, when the association of NSF with gadolinium administration became public, has greatly diminished.

Among MedWatch NSF cases where GFR is reported in the narrative, only one case reports GFR at the time of administration of a GBCA that would indicate less-than-severe renal dysfunction. This suggests that NSF occurs almost exclusively among patients with severe renal insufficiency.

The analysis of disproportional reporting from the AERS data within the gadolinium product class, shows safety signals for Omniscan and Optimark. This was not an analysis of absolute risk, but a comparison of reporting rates compared to reports of other adverse events associated with these products. Reports of nephrogenic system fibrosis (NSF) are more frequent than expected with these two contrast agent drugs, when compared to the other three.

7 LITERATURE

7.1 INTENT OF THE REVIEW

As for the other analyses conducted within the Office of Surveillance and Epidemiology, the literature review was conducted to evaluate whether the risk of NSF varies across GBCAs. Additionally, this review summarizes the literature findings to determine if recent liver transplantation is an independent risk factor of NSF and if acute dialysis immediately after GBCA exposure prevents NSF in patients who are not on chronic dialysis.

7.2 MATERIALS AND METHODS

A systematic literature search was conducted in PubMed for publications in English language published between January 1, 2000 and July 31, 2009. A second literature search was conducted in the same way to identify new publications from July 31, 2009 to October 21, 2009. The keywords used in this search included "gadolinium", "Omniscan", "gadodiamide", "Magnevist", "gadopentetate", "Optimark", "gadoversetamide", "Prohance", "gadoteridol", "Multihance", "gadobenate", "nephrogenic systemic fibrosis", and "nephrogenic fibrosing dermopathy".

All abstracts were reviewed for study design and relevance to this review. Case reports and review studies were excluded from this review because they do not contain population-based or original NSF risk estimates. The full text of observational cohort studies, case-control studies, and case series were reviewed and those studies that contain NSF risk estimates formed the basis of this literature review. To evaluate the risk of NSF, only studies that contained quantifiable, product-specific estimates were included.

7.2.1 Classification of studies

To evaluate the degree of association between NSF and GBCAs in comparable study populations, the studies included in this review were classified by the study subjects' renal function as shown in Table 1. The GFR reported in some studies was estimated glomerular filtration rate (eGFR) that was calculated with the Modification of Diet in Renal Disease Study Group equation.

7.3 RESULTS

7.3.1 Selection of articles for detailed review

A total of 182 articles related to GBCAs and their risk of NSF were obtained in the first literature search. After screening for relevant information to quantify the risk of NSF for GBCAs, a total of 31 studies were selected (Appendix 7). The analysis of differential NSF risk associated with specific GBCAs excluded studies that did not describe the specific GBCAs used (n=4) or did not include detailed exposure or case information (n=6). The second literature search found two studies that contain product-specific NSF risk estimates. Thus, the final review of the differential risk included three prospective cohort studies, 14 retrospective cohort studies, five case-control studies, and one case series (total n=23).

7.3.2 Severity of kidney disease and risk of NSF

All NSF patients identified in this review had stage 4-5 CKD or acute renal failure, and were often on dialysis. This review has not found any study reporting NSF in patients with normal kidney function or CKD stages 1-3. For example, a cohort study of 190 Omniscan-exposed patients with various degrees of chronic renal insufficiency found no NSF cases among 88 patients with CKD stage 1-4. However, 18% (95% confidence interval (CI) 11%-27%) of 102 CKD stage 5 patients developed NSF[29]. Similarly, a recent review reported that 80% of 124 NSF cases had end-stage renal disease (ESRD) on dialysis, 9% had stage 5 CKD not on dialysis, 3% had stage 4 CKD, and 8% had acute renal failure[30].

7.3.3 NSF risk by GBCA product and by CKD stage

Ten studies directly compared NSF risk across GBCAs (Table 6 and Table 7). Table 6 presents the prevalence or incidence of NSF among patients with stage 5 CKD while Table 7 presents the prevalence or incidence of NSF among more heterogeneous patient populations.

In Table 6, four cohort studies, one prospective and three retrospective, compared the prevalence of NSF among Omniscan, Magnevist, and Multihance users who had stage 5 CKD or were on dialysis.

- Two retrospective cohort studies found that Omniscan was associated with a higher prevalence of NSF than Magnevist (3.2% vs. 0%, and 10% vs. 0%)[31,32]
- In contrast, the third study, a prospective cohort, found that Magnevist users had a higher prevalence of NSF than Omniscan (5% vs. 0%)[33]. However, there were only 4 patients exposed to Omniscan in this study.
- A third retrospective cohort study, Altun et al.[34], reported that the prevalence of NSF reduced from 2.88% to zero among dialysis patients after the study institution changed the Omniscan to Multihance and Magnevist and adopted a restrictive GBCA policy.

Table 6 also outlines two case-control studies.

- One case-control study reported an odds ratio (OR) of 9.83 (95% CI, 2.09-46.25) of developing NSF among patients who were exposed to Omniscan compared to those unexposed and an OR of 1.82 (95% CI, 0.33-10.15) among patients who were exposed to Optimark compared to those unexposed[35].
- The last study in Table 6 reported a higher prevalence of NSF associated with Omniscan (2.7%) use compared to 0% among Magnevist, Multihance, Gadovist, or Vasovist users. Of note, the prevalence of NSF was reported as per contrast enhanced imaging procedure

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[29] Rydahl C, Thomsen HS, Marckmann P. High prevalence of nephrogenic systemic fibrosis in chronic renal failure patients exposed to gadoliamide, a gadolinium-containing magnetic resonance contrast agent. Investigative Radiology. 2008; 43 (2): 141-144.
[30] Grobner T, Prischl FC. Patient characteristics and risk factors for nephrogenic systemic following gadolinium exposure. Seminars in Dialysis. 2008; 21(2): 135-139.
[31] Wiginton CD, Kelly B, Oto A, et al. Gadolinium-based contrast exposure, nephrogenic systemic fibrosis, and gadolinium detection in tissue. AJR. 2008; 190: 1060-1068
[32] Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology. 2008; 248(3): 807-816
[33] Schietinger BJ, Brammer GM, Wang H, et al. Patterns of late gadolinium enhancement in chronic hemodialysis patients. Journal of American Cardiovascular Imaging. 2008; 1(4): 450-456
[34] Altun E, Martin DR, Wertman R, et al. Nephrogenic systemic fibrosis: change in incidence following a switch in gadolinium agents and adoption of a gadolinium policy-report from two U.S. universities. Radiology. 2009 Oct. 7. Access on Oct. 20, 2009 at http://radiology.rsna.org/content/early/2009/10/06/radiol.2533090649.long
[35] Kallen AJ, Jhung MA, Cheng S, et al. Gadolinium-containing magnetic resonance imaging contrast and nephrogenic systemic fibrosis : a case-control study. American Journal of Kidney Disease. 2008; 51(6): 966-975

instead of unique patient[36]. Since some patients may take multiple exams, the prevalence of NSF per patient in the Omniscan group may be higher than 2.7%.

Three studies listed in Table 7 examined the prevalence or incidence of NSF among all patients who had exposure to Omniscan, Magnevist, Prohance, Multihance, or Vasovist (this last agent is not considered in the current document).

- Compared with Magnevist, Omniscan was associated with higher risk of NSF (OR=13.17, 95% CI 4.66-37.20) in one study with a large sample size of 82,260 and 135,347 patients in the Omniscan and Magnevist cohorts, respectively[37].
- In the Prince[38] study of the general patient population, the prevalence of NSF was 0.02%, 0.04%, respectively, for Omniscan and Multihance users, while the prevalence was 0% for both Magnevist and Prohance. This study further broke down the prevalence of NSF among different subgroups of study subjects. In the subgroup of CKD4, the prevalence of NSF was 0.6% for Omniscan compared to 0% for Magnevist, Prohance, or Multihance. Similarly, in patients whose estimated GFR (eGFR) was less than 30 ml/min without acute renal failure, the prevalence of NSF was 0.7% for Omniscan users compared to 0% for Magnevist, Prohance, or Multihance users. However, for those who had acute renal failure at the time of GBCA administration, the prevalence of NSF was 10% among Omniscan users (n=101), 33% among Multihance users (n=3), and 0% among Magnevist users (n=27).
- Chrysochou[39] did not find any case of NSF in patients who received Omniscan, Magnevist, or Vasovist.

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[36] Collidge TA, Thomson PC, Mark PB, et al. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis : retrospective study of a renal replacement therapy cohort. Radiology. 2007; 245(1): 168-175

[37] Wertman R, Altun E, Martin DR, et al. Risk of nephrogenic systemic fibrosis: evaluation of gadolinium chelate contrast agents at four American Universities. Radiology. 2008; 248(3): 799-806

[38] Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology. 2008; 248(3): 807-816

[39] Chrysochou C, Buckley DL, Dark P, et al. Gadolinium-enhanced magnetic resonance imaging for renovascular disease and nephrogenic systemic fibrosis: critical review of the literature and UK experience. Journal of Magnetic Resonance Imaging. 2009; 29: 887-894

The other three studies included in Table 4 were conducted in patients with CKD 3-5 and 2-5.

- Hoppe et al.[40] reported that the prevalence of NSF was 4% for Omniscan users and neither of the single patient used Magnevist nor the single patient used Gadovist developed NSF.
- Similarly, Altun et al.[34] reported that the prevalence of NSF was 3.03% in Omniscan users and the prevalence reduced to zero when Omniscan was replaced by Multihance and Magnevist and the adoption of a restrictive GBCA policy.
- No cases of NSF were found in the last study listed in Table 7 that examined the prevalence of NSF in Magnevist, Omniscan, Multihance, Vasovist, and Dotarem among patients with CKD stage 2-5[41].

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[40] Hoppe H, Spagnuolo S, Frochlich JM, et al. Retrospective analysis of patients for development of nephrogenic systemic fibrosis following conventional angiography using gadolinium-based contrast agents. Eur Radiol. 2009

[41] Janus N, Launay-Vacher V, Karie S, et al. Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: results of the FINEST study. European Journal of Radiology. 2008, doi: 10.1016/j.ejrad.2008.11.021

Table 6. NSF risk among patients with stage 5 CKD by products among studies with multiple GBCAs

Author Year Study Design	Study Population	Follow-up Time from Exposure (month)	GBCAs	GBCA Dosage (mmol/Kg)	Number of Exposed	Number of Cases	Prevalence of NSF	Odds Ratio (OR)	Study Limitations
Altun * 2009 RC	Dialysis pts	<=40	Omniscan	Not reported	312	9	2.88%		Omniscan was used prior to the adoption of a restrict GBCA policies that contributed substantially to the decrease in the incidence of NSF post-adoption; short follow-up with Magnevist/Multihance cohorts; Multihance was used half dose in patients with risk factors and standard dose in pts without risk factors; Magnevist was used at standard dose
		9	Magnevist/ Multihance		402	0	0		
Schietinger 2008 PC	HD pts >50 yrs	23+/-3	Omniscan	0.15	4	0	0		The case associated with Magnevist received 2 prior MRAs with unknown Gd; Small sample size.
			Magnevist	0.15	20	1	5%		
§ Wiginton 2008 RC	Dialysis pts	<=120	Omniscan	Cases: cumulative doses 0.16-0.43	54	2	3.7%		Small sample size; dose unknown; Magnevist was discontinued in 2000; NSF in Magnevist users may be under-diagnosed.
			Magnevist	Not reported	9	0	0		
			Omniscan + Magnevist	Not reported	9	0	0		
Prince* 2008 RC	CKD 5	<=36	Omniscan	>=0.1	100	10	10%		Multiple exposures were not captured completely or considered in the analysis; GBCA was not specifically documented for every MR exam; mild cases may not have been identified
			Magnevist	>=0.1	14	0	0		
			Optimark	Not reported	Not reported	3	Not reported	OR=1.82 (95% CI, 0.33-10.15) (Optimark exposed vs. unexposed)	

Author Year Study Design	Study Population	Follow-up Time from Exposure (month)	GBCAs	GBCA Dosage (mmol/Kg)	Number of Exposed	Number of Cases	Prevalence of NSF	Odds Ratio (OR)	Study Limitations
Kallen 2008 CC	Inpatients and outpatients on dialysis	Examined exposures in 6-12 months before NSF detection	Omnisacan	Not reported	Not reported	10	Not reported	OR=9.83 (95% CI, 2.09-46.25) (Omniscan exposed vs. unexposed)	Small sample size; misclassification of exposure; unidentifiable gadolinium exposure was noted by authors; short follow-up time (less than 5 months) for OptiMark users
			Optimark	Not reported	Not reported	3	Not reported	OR=1.82 (95% CI, 0.33-10.15) (OptiMark exposed vs. unexposed)	
§ Collidge 2007 ** CC	Dialysis-dependent CKD 5	<=72	Omniscan	Median dose 30ml	480	13	2.7%		Small sample size for all other GBCAs except Omniscan; one case had unidentifiable exposure to gadolinium; Cannot exclude some NSF cases were not diagnosed
			Magnevist	15 ml	13	0	0		
			MultiHance	15 ml	41	0	0		
			Gadovist	15 ml	6 p	0	0		
			Vasovist	10 ml	2 p	0	0		

* The Prince and Altun studies appear in Table 6 and Table 7

** Imaging procedures were the unit of analysis for 421 exposed patients

Abbreviations: PC: prospective cohort; RC: retrospective cohort; CC: Case-control; HD: Hemodialysis; PD: Peritoneal dialysis; eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease; NR: not reported

§ Studies had made efforts to minimize the misclassification bias associated with GBCA exposure during study time. However, this did not exclude the possibility that patients may have additional exposure outside the study institution or prior to the study look back period.

Table 7. NSF risk in more heterogeneous patient population among studies with multiple GBCAs

Author Year Study Design	Follow-up Time from Exposure (month)	Study Population	GBCAs	GBCA Dosage (mmol/Kg)	Number of Exposed	Number of Cases	Prevalence of NSF	Odds Ratio (OR)	Comments on Study
Hoppe 2009 RC	28 (1-84)	CKD 3-5	Omniscan	0.1-0.53	25	1	4%		Dermatology reports were available for only 11 patients. There may be more NSF cases in the other 16 patients; small sample size
			Magnevist	0.23	1	0	0		
			Gadovist	0.3	1	0	0		
Altun* 2009 RC	<=84	CKD 3-5 & acute renal failure	Omniscan	Not reported	925	28	3.03%		Omniscan was used prior to the adoption of a restrict GBCA policies that contributed substantially to the decrease in the incidence of NSF post-adoption; short follow-up with Magnevist/Multihance cohorts; Multihance was used half dose in patients with risk factors and standard dose in pts without risk factors; Magnevist was used at standard dose
	9		Magnevist/ Multihance		147	0	0		
Chrysochou 2009 RC	29 (3-102)	90% CKD 3-5 patients (Mean eGFR of 31 ml/min, range 5-133)	Omniscan	0.1, 0.2	37	0	0		Pts with less than 11 weeks follow-up were excluded; small sample size for Omniscan; multiple exposures were not captured because only renal MRAs were included
			Magnevist	0.1, 0.2	521	0	0		
			Vasovist	0.1, 0.2	4	0	0		
§ Wertman 2008 RC	<=72	All pts exposed at tertiary care centers with renal transplant and dialysis	Omniscan	Mean cumulative dose 0.36	82260	32	0.039%	OR=13.17 (95% CI 4.66-37.2) (Omniscan vs. Magnevist)	Study with extensive efforts to identify all exposures. Those included in the analysis were exposed to the specified agents only. Large sample size; NSF may be under-
			Magnevist	0.43	135347	4	0.003%		

Author Year Study Design	Follow-up Time from Exposure (month)	Study Population	GBCAs	GBCA Dosage (mmol/Kg)	Number of Exposed	Number of Cases	Prevalence of NSF	Odds Ratio (OR)	Comments on Study
		services							diagnosed; no subgroup analysis

Table 7: NSF risk in more heterogeneous patient population among studies with multiple GBCAs (continued)

Author Year Study Design	Follow-up Time from Exposure (month)	Study Population	GBCAs	GBCA Dosage (mmol/Kg)	Number of Exposed	Number of Cases	Prevalence of NSF	Odds Ratio (OR)	Comments on Study
Prince * 2008 RC	<=36	All pts exposed	Omniscan	>=0.1	71441	14	0.02%		Multiple exposures were not captured completely or considered in the analysis; GBCA was not specifically documented for every MR exams; mild cases may not have been identified
			Magnevist	>=0.1	8669	0	0		
			Prohance	>=0.1	226	0	0		
			Militance	>=0.1	2785	1	0.04%		
		CKD 4	Omniscan	>=0.1	311	2	0.6%		
			Magnevist	>=0.1	73	0	0		
			Prohance	>=0.1	9	0	0		
			Multihance	>=0.1	3	0	0		
		CKD 4-5 with no acute renal failure	Omniscan	>=0.1	552	4	0.7%		
			Magnevist	>=0.1	94	0	0		
			Multihance	>=0.1	9	0	0		
		Acute renal failure	Omniscan	>=0.1	101	10	10%		
			Magnevist	>=0.1	27	0	0		
			Multihance	>=0.1	3	1	33%		
Janus 2008 RC	4	CKD 2-5 (53.6% CKD 5)	Dotarem	Not reported	176	0	0		Short follow-up time; multiple exposures not counted
			Magnevist	Not reported	46	0	0		
			Omniscan	Not reported	7	0	0		
			Multihance	Not reported	3	0	0		

* The Prince and Altun studies appear in Table 6 and Table 7
Abbreviations: PC: prospective cohort; RC: retrospective cohort; CC: Case-control; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; MRA: magnetic resonance angiography; NR = not reported
§ Studies had made efforts to minimize the misclassification bias associated with GBCA exposure during study time. However, this did not exclude the possibility that patients may have additional exposure outside the study institution or prior to the study look back period.

Studies that assessed the incidence or prevalence of NSF associated with a single GBCA are presented in Table 8 and Table 9. Table 8 lists 13 studies done in populations with stage 4-5 CKD or on dialysis, while Table 9 presents four studies that investigated the prevalence of NSF among patients with stage 1-4 CKD and other patients without renal failure.

In Table 8, nine, three, and one study examined patients who were administered Omniscan, Magnevist, and Prohance, respectively. No single-agent studies regarding Optimark or Multihance were found in the literature search. The prevalence of NSF ranged from 0.38% to 29.6% among dialysis patients exposed to Magnevist and was 0.07% for those patients with CKD 4 and 5 but not on dialysis. The NSF prevalence associated with Omniscan ranged from 0.27% among CKD 4, acute renal failure, or hemodialysis patients without infections to 56% of ESRD patients on hemodialysis. The only single-agent study of Prohance did not find any NSF case among 141 hemodialysis patients.

There were four studies of a single GBCA in patients with CKD 1-4 or normal kidney function. As shown in Table 9, the only agent studied was Omniscan and none of the studies found NSF cases.

Table 8. NSF risk assessment among patients with stage 5 CKD by products in studies with a single GBCA

GBCAs	Author Year Study Design (see note)	Follow-up Time from Exposure (month)	Study Population	GBCA Dosage (mmol/Kg)	Number of Exposed	Number of Cases	Prevalence/ Incidence of NSF	Study Limitations
Magnevist	§ Steen 2009 PC	Median 16	Pts on HD or PD	0.14-0.17	136	1	0.74%	Other exposures were not mentioned
	§ Hope 2009 RC	21.4+/-11.2	Pts on HD	NR	530	2	0.38%	Pts who died within 1 month of exposure or left system within 3 months were excluded; lower average dose and number of exams than other studies; mild cases may be missed; can't exclude pts received outside exposure
			CKD 4 and 5 not on dialysis	NR	2862	2	0.07%	
	§ Todd 2007 PC	<=12	Pts on HD	NR	54	16	29.6%	One case did not have documented Magnevist exposure suggesting the study failed to capture all exposures; 12 cases were identified by skin examination, but not biopsy confirmed; small sample size
Prohance	§ Reilly 2008 RC	19 +/-15.8	Pts on HD	NR	141	0	0	Mild cases may be missed; some patients may not have adequate follow-up time to detect NSF
Omniscan	§ Chen 2009 RC	15.4+/-7.62	Pts on HD or PD	0.1, 0.2	81	1	1.23% all exposed 7.1% (1/14) in PD 0% (0/67)in HD	NSF cases may be underestimated
	§ Bridges 2009 RC	>= 12 (average nearly 36 mons)	CKD 5 with a high single dose (>=40ml)	Median 40 mmol, range 25-70 mmol	11	1	9.1% (95% CI 0.23%-41.3%)	Small sample size; pts with < 1 yr follow-up were excluded
	§ Golding 2008	<=48	Infected CKD 4-5,	0.1-0.31	80	5	6.3% (95% CI 2.7%-	NSF cases were prospectively identified

GBCAs	Author Year Study Design (see note)	Follow-up Time from Exposure (month)	Study Population	GBCA Dosage (mmol/Kg)	Number of Exposed	Number of Cases	Prevalence/ Incidence of NSF	Study Limitations
	RC		acute renal failure, or HD pts				13.8%)	(strength); but some patients with NSF may not have been seen by diagnosing physicians; pts in whom a biopsy was not obtained were excluded, thus the NSF cases may be underestimated
			Uninfected CKD 4-5, acute renal failure, or HD pts	0.1-0.31	752	2	0.27% (95% CI 0.07%-0.96%)	
	§ Rydahl 2008 RC	29 (16-43)	CKD 5	Mean cumulative dose 24.0 mmol	102	18	18% (95% CI 11%-27%)	Most pts received higher dosages of 0.3 mmol/Kg in this study
	§ Othersen 2007 RC	<=60	Pts on HD or PD	7.5-10 mmol in cases	261	4	1.53%	Other exposure outside the study institution cannot be excluded; cases may be underestimated
	§ Broome * 2007 RC	<=72	Pts on dialysis	0.1-0.2; 0.2 in cases	301	12	4.0%	Prevalence unit was not unique patients; cases may be underestimated
	§Lauenstein 2007 CC	<=41	Pts on dialysis	Average cumulative dose of 30.5 mmol in cases	312	8	2.6%	The exposure data were collected between the date of first and last NSF case diagnosis that may over estimate the prevalence; other exposure was not explored
	§Marckmann 2006 CC	6	ESRD pts	Cumulative dose 11-63 mmol in cases	370	13	3.5%	Cannot exclude cases received outside gadolinium exposure
	Grobner 2006 CC	<=24	HD	NR	9	5	56% (95% CI 26%-81%)	Small sample size

* Unit of analysis was medical imaging exam

Abbreviations: PC: prospective cohort; RC: retrospective cohort; CC: Case-control; CS: Case series; HD: Hemodialysis; PD: Peritoneal dialysis; eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease; ESRD: End-stage renal disease (a term defined by the Federal government to indicate chronic treatment by dialysis or renal transplantation); NR = not reported

§ There was only one agent used during the study period. However, this did not exclude the possibility that patients may have additional exposure outside the study institution or prior to the study look back period.

Table 9. NSF risk assessment among patients with stage 1-4 CKD and other non-renal failure patients by products in studies on single GBCA

GBCAs	Author Year Study Design (see note)	Follow-up Time from Exposure (month)	Study Population	GBCA Dosage	Number of Exposed	Number of Cases	Prevalence/ Incidence of NSF	Study Limitations
Omniscan	§ Rydahl 2008 RC	29 (16-43)	CKD 1-4	Mean cumulative dose 24.0 mmol	88	0	0	Most pts received higher dosages of 0.3 mmol/Kg in this study
	§ Othersen 2007 RC	<=60	CKD 3-4	7.5-10 mmol	592	0	0	Other exposure outside the study institution cannot be excluded; cases may be underestimated
	§ Bridges 2009 RC	>= 12	CKD 3-4 with a high single dose	Median 45 mmol, range 20-100 mmol	50	0	0	Small sample size; pts with < 1 yr follow-up were excluded
	§ Golding 2008 RC	<=48	CKD1-3 and other non-renal failure pts	0.1-0.31	50,830	0	0	NSF cases were prospectively identified (strength); but some patients with NSF may not have been seen by diagnosing physicians; pts in whom a biopsy was not obtained were excluded, thus the NSF cases may be underestimated

Abbreviations: PC: prospective cohort; RC: retrospective cohort; CC: Case-control; CKD: Chronic kidney disease

§ There was only one agent used during the study period. However, this did not exclude the possibility that patients may have additional exposure outside the study institution or prior to the study look back period.

7.3.4 Additional findings

7.3.4.1 Dose Response

There is evidence in the literature suggesting that either a single high dose or high lifetime dose of GBCAs, or both, may be independent risk factors of NSF. Othersen et al.[42] found that the OR of developing NSF increased from 6.7 (95% CI, 1.54-53.97) in patients with a single exposure to 44.5 (95% CI, 2.36-2913) in patients with multiple exposure to Omniscan. Rydah et al.[43] reported the prevalence of NSF was 12% with one Omniscan exposure, 36% with two exposures, and 25% with three exposures. Shabana et al.[44] reported a prevalence of 2.7% in patients who had 1-2 exposures and 4.6% in patients who had 3-4 exposures to unspecified gadolinium agents. Kallen et al.[45] described that the OR increased in a stepwise fashion from 4.41 (95% CI, 1.01-19.24) for having one gadolinium exposure to 14.10 (95% CI, 2.06-96.12) with 2-3 exposures and to 21.46 (95% CI, 2.08-221.97) with four or more exposures. Prince et al.[46] reported an incidence of 0.2% and 0.6% in patients who were exposed to a single high dose of Omniscan and Multihance, respectively. However, the same study did not find any NSF cases in 5725 patients who received multiple standard 0.1 mmol/Kg doses.

7.3.4.2 Liver transplantation and the risk of NSF

This review identified three studies that mentioned liver transplantation and NSF (Table 10). Bridges et al.[47] reported that no NSF diagnosis was made in six liver transplantation patients who received Omniscan during a period of acute renal failure. Two other studies mentioned that several NSF cases had recent liver transplantation[48, 49]. However, the total number of patients with recent liver transplantation who had exposure to gadolinium was not provided in the articles. Therefore, the risk of NSF could not be assessed among patients with liver transplantation in the currently available literature.

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[42] Othersen JB, Maize Jr. JC, Woolson RF, et al. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrol Dial transplant. 2007; 3179-3185.

[43] Rydahl C, Thomsen HS, Marckmann P. High prevalence of nephrogenic systemic fibrosis in chronic renal failure patients exposed to gadoliamide, a gadolinium-containing magnetic resonance contrast agent. Investigative Radiology. 2008; 43 (2): 141-144.

[44] Shabana WM, Cohan RH, Ellis JH, et al. Nephrogenic systemic fibrosis: a report of 29 cases. AJR. 2008; 190: 736-741.

[45] Kallen AJ, Jhung MA, Cheng S, et al. Gadolinium-containing magnetic resonance imaging contrast and nephrogenic systemic fibrosis : a case-control study. American Journal of Kidney Disease. 2008; 51(6): 966-975.

[46] Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology. 2008; 248(3): 807-816.

[47] Bridges MD, St. Amant BS, McNeil RB, et al. High-dose gadodiamide for catheter angiography and CT in patients with varying degrees of renal insufficiency: prevalence of subsequent nephrogenic systemic fibrosis and decline in renal function. American Journal of Radiology. 2009; 192: 1538-1543.

[48] Perez-Rodriguez J, Lai S, Ehst BD, et al. Nephrogenic systemic fibrosis : incidence, associations, and effect of risk factor assessment-report of 33 cases. Radiology. 2009; 250(2): 371-377.

[49] Shabana WM, Cohan RH, Ellis JH, et al. Nephrogenic systemic fibrosis: a report of 29 cases. AJR. 2008; 190: 736-741.

Table 10. NSF risk among those patients with recent liver transplantation

Study	Number of NSF cases	Number of Patients Exposed	Key Findings
Bridges 2009[47]	0	6	No NSF diagnosis was made in six liver transplantation patients who received Omniscan during acute renal failure period
Perez-Rodriguez 2009[48]	5	Not reported	Five out of 33 NSF cases were liver transplant patients who developed NSF within 3 months after GBCA exposure in the form of acute renal failure
Shabana 2008[49]	8	Not reported	Eight out of 26 NSF cases had liver transplantation

7.3.4.3 Acute dialysis and NSF prevention

Six studies describing acute dialysis therapy after gadolinium exposure are summarized in Tables 11 through Table 13 (one study is included in two tables). Among patients who were not on chronic dialysis (Table 11), one study found that no patients who underwent hemodialysis on the same day of GBCA administration developed NSF while there were eight cases of NSF in patients who had acute renal failure but did not receive dialysis until 48 hours later[50]. The other study also reported that one patient developed NSF despite undergoing dialysis within 48 hours after exposure[51].

Table 11. Effect of acute dialysis among patients who were not on chronic dialysis

Study	Number of NSF Case	Number of Patients Exposed	Lag time between GBCA dose and Dialysis (hours)	Key Findings
Prince 2008[50]	0	32	<24	No patients who underwent hemodialysis the same day (n=32) developed NSF; The highest incidence of NSF (19%) was observed in patients with acute renal failure who received GBCA when their serum creatinine level was increasing but did not undergo hemodialysis for at least 2 days afterward.
	8	Not reported	>48	
Wiginton 2008[51]	1	Not reported	48	This patient had acute renal failure when Omniscan was administrated

In Table 12, all studies reported NSF cases in patients who were on chronic dialysis and received dialysis at least one day after exposure.

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[50] Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology. 2008; 248(3): 807-816.
[51] Wiginton CD, Kelly B, Oto A, et al. Gadolinium-based contrast exposure, nephrogenic systemic fibrosis, and gadolinium detection in tissue. AJR. 2008; 190: 1060-1068.

Table 12. Effect of acute dialysis among patients who were on chronic dialysis

Study	Number of NSF case	Number of Patients Exposed*	Lag time between GBCA dose and Dialysis (hours)	Key Findings
Prince 2008[50]	1	Not reported	>24	For patients with an eGFR < 15, hemodialysis helped to prevent NSF
Golding 2008[52]	6	Not reported	>24	All six patients were dialyzed 1 day after gadolinium exposure
Lauenstein 2007 [53]	4	Not reported	<72	Within three days, two NSF cases received dialysis once and two received dialysis three times

In Table 13, two studies reported that patients developed NSF despite the fact that they were dialyzed on the same day of gadolinium exposure[54, 55]. However, it is unknown whether those patients were on chronic dialysis or not.

Table 13. Effect of acute dialysis among patients with unknown dialysis status

Study	Number of NSF Case	Number of Patients Exposed*	Lag time between GBCA dose and Dialysis (hours)	Key Findings
Broome 2007[54]	3	Not reported	<24	Among all 12 cases, eight patients were dialysis-dependent and four had acute renal failure. Ten cases were dialyzed within 2 days. However, it is unknown how many of those 10 patients were on chronic dialysis. Three patients had received daily dialysis for three consecutive days starting on the day of Omniscan administration, but dialysis did not prevent their development of NSF
	7	Not reported	48	
Perez-Rodriguez 2009[55]	7	Not reported	<24	Seven patients underwent one hemodialysis session within 24 hours of GBCA exposure and still developed NSF

7.3.4.4 Off-label Use

The only FDA-approved indication for GBCAs is use as a contrast agent in MRI at an initial dose of 0.1 mmol/Kg for all products[56]. A second dose of 0.2 mmol/Kg may be given shortly after the first dose in adult patients suspected of having poorly enhancing lesions for Prohance and Omniscan.

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[52] Golding LP, Provenzale JM. Nephrogenic systemic fibrosis: possible association with a predisposing infection. AJR. 2008; 190: 1069-1075

[53] Lauenstein TC, Salman K, Morreira R, et al. Nephrogenic systemic fibrosis : center case review. Journal of magnetic resonance. 2007; 26: 1198-1203

[54] Broome DR, Girguis MS, Baron PW, et al. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. AJR. 2007;188: 586-592.

[55] Perez-Rodriguez J, Lai S, Ehst BD, et al. Nephrogenic systemic fibrosis : incidence, associations, and effect of risk factor assessment-report of 33 cases. Radiology. 2009; 250(2): 371-377.

[56] Product labels for Omniscan, Magnevist, MultiHance, OptiMark, and ProHance, Accessed via drugs@fda.gov.

Although none of these five products were approved for indications other than MRI, this literature review identified that these agents were also used for magnetic resonance angiography (MRA), arteriography, and venography (MRV).[32,39,47,57,58]

7.4 DISCUSSION (LITERATURE)

7.4.1 NSF differential risk based on literature review

This epidemiology review evaluated the NSF risk associated with GBCAs based on 23 studies that reported product-specific NSF risk estimates. Omniscan was investigated in 19 studies, while Magnevist, Multihance, Prohance were examined in 12, 4, and 2 studies, respectively. There was only one study that examined Optimark. There were more studies in the current epidemiological literature we reviewed that reported a higher prevalence of NSF for Omniscan than for other GBCAs such as Magnevist, Optimark, and Multihance. This trend was most apparent in studies that examined patients with stage 5 CKD. In a more general population, the trend was less apparent since the prevalence of NSF was lower. No NSF case had been reported in Prohance users in the epidemiological studies included in this review. However, all the studies had significant shortcomings that severely limited the interpretation of the data to reach a firm conclusion about the differential risk of NSF among the GBCAs. These are noted in Section 7.4.2.

There were exceptions to the seemingly higher risk of NSF associated with Omniscan than other GBCAs. Magnevist was associated with higher prevalence of NSF compared to Omniscan among patients on hemodialysis (5% vs. 0%) in a single study conducted by Schietinger[59]. It is worth noting that there were only four patients in the Omniscan cohort compared to 20 patients in the Magnevist cohort. In the Prince[60] study, patients with acute renal failure had a higher prevalence with Multihance than Omniscan (33% vs. 10%) although patients with CKD 4 or 5 had a higher prevalence of NSF with Omniscan than Multihance (0.7% vs. 0%). The other two studies on Multihance by Janus[61] and Collidge[62] did not find any NSF cases in limited sample sizes of 3 patients and 41 imaging procedures.

This review noticed a disproportional relationship between sales data and prevalence of NSF for Omniscan and Magnevist. Penfield[63] mentioned that the frequent association of NSF with Omniscan (83% of cases reported in the literature) cannot be explained by its market share, which was around 26% in the US from July 2005 to September 2007, while Magnevist had the highest

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[57] Reilly RF. Risk for nephrogenic systemic fibrosis with gadoteridol (ProHance) in patients who are on long-term hemodialysis. Clin J Am Soc nephrol. 2008; 3: 747-751

[58] Kane GC, Stanson AW, Kalnicka D, et al. Comparison between gadolinium and iodine contrast for percutaneous intervention in atherosclerotic renal artery stenosis : clinical outcomes. Nephrol Dial Transplant. 2008; 23: 1233-1240

[59] Schietinger BJ, Brammer GM, Wang H, et al. Patterns of late gadolinium enhancement in chronic hemodialysis patients. Journal of American Cardiovascular Imaging. 2008; 1(4): 450-456

[60] Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology. 2008; 248(3): 807-816

[61] Janus N, Launay-Vacher V, Karie S, et al. Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: results of the FINEST study. European Journal of Radiology. 2008, doi: 10.1016/j.ejrad.2008.11.021

[62] Collidge TA, Thomson PC, Mark PB, et al. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis : retrospective study of a renal replacement therapy cohort. Radiology. 2007; 245(1): 168-175

[63] Penfield JG, Reilly RF. Nephrogenic systemic fibrosis risk: is there a difference between gadolinium-based contrast agents? Semin Dial. 2008; 21: 129-134

market share of 54% in the same period but had smaller percentage of cases linked to its use. FDA drug use analysis conducted for this review also showed that the market share for Omniscan and Magnevist were around 29%, and 47%, respectively, in the US from January 2005 to June 2009.[64]

7.4.2 Study Limitations

Significant limitations in the studies that were included in this review resulted in major difficulties in assessing the differential risk of NSF across GBCAs and adversely influence the validity and generalizability of the study results. Those limitations are discussed below.

7.4.2.1 Heterogeneous Patient Population

In this review, many studies examined the prevalence of NSF among various subgroups of renal patients. Those subgroups include patients with stage 5 CKD, patients with stage 4-5 CKD, patients with stage 1-5 CKD, patients on hemodialysis or peritoneal dialysis, patients with acute renal failure, ESRD patients with or without infection, or a mix of several of these categories. Some other studies assessed the risk of NSF among all patients who had exposure to certain GBCAs regardless of CKD status.

This literature review found that all NSF cases have been identified in patients with CKD 4-5 or acute renal failure, but not in other subsets of the general population. Clearly, the incidence and prevalence of NSF are influenced by the renal function of the study patient population. Therefore, a quantitative comparison of the estimated NSF risk associated with GBCAs across studies is not appropriate unless the study populations are comparable in terms of renal function.

However, direct comparison of product risk could be done in studies that examined multiple GBCAs (those studies were presented in Table 6 and Table 7). Since the risk of NSF associated multiple GBCAs were examined within the same study population in each study, the risk estimates across the study GBCAs can be compared directly within each study. Because of these issues with heterogeneous study populations, this review presented the risk estimates by CKD stage in order to make the study populations more comparable.

7.4.2.2 Multiple Exposures

The majority of studies included in this review define the GBCA exposure status based on patients' MR imaging and other medical records. Due to the nature of retrospective study designs, some studies only looked at gadolinium exposure in a limited time period prior to the NSF diagnosis. There may have been additional exposure to the same or other types of gadolinium agents beyond the study timeframe and/or outside the study institution. Therefore, patients may have had more exposures to GBCAs prior to the development of NSF that were not captured in the studies. Reports of NSF in patients without gadolinium exposure in some studies may indicate the failure to identify all gadolinium exposures in those studies. Under these conditions, it is impossible to determine with certainty which agent caused the development of NSF. Thus, the estimated attributable risk of NSF for the observed GBCAs, usually the most recent one, may be biased away from the null (it may be too high, as it may reflect exposure to a previously-administered agent).

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[64] Data source: IMS Health, IMS National Sales Perspectives™, Year 2005-2009, extracted 8-09. Files: 0908gado.xls and 0908gbca.xls

7.4.2.3 Misclassification of Exposure

In addition to the issue with confounded exposure, retrospective study designs may also be susceptible to recording errors or missing information in the medical records that could lead to misclassification of GBCA exposure status. Validation of exposure becomes even more difficult when several GBCA products have been used within the risk window in the study institution. For example, an imaging center may continue to record the name of a previous GBCA in the log book after the formulary had changed to a different GBCA.

Since the latency period can range from days to years in NSF development, the gadolinium exposure of interest may have happened prior to the start of studies. Therefore, with the concern that there could be additional exposure to other types of gadolinium agents prior to the study time or outside the study institution, misclassification of gadolinium exposure status was a potential bias in almost all studies included in this review. Instead of trying to capture the exposure information as much as possible, some studies attributed the NSF risk to the most recent GBCA that the patients have been exposed to. Because of the misclassification bias, the estimated NSF prevalence for GBCAs in the literature may not reflect the true risk.

7.4.2.4 Varying Exposure Dosages

Depending on the indication and study population, the average or median GBCA dosage was higher in some studies than others. Since there may be a dose-response relationship between GBCA exposure and NSF risk, not adjusting for dose when comparing NSF prevalence across studies may be lead to biased risk estimates. However, it is very difficult to track all GBCA exposures and dosages within a reasonable exposure risk window as many studies acknowledged.

7.4.2.5 Small Sample Size and Unbalanced Comparison Groups

Many studies had very small sample size as they were conducted in a single institution with limited patient population. These small sample sizes limited the study's power to identify significant difference in NSF risk across GBCAs studied. Some other studies have large number of patients with exposure to one or two GBCAs, but very few patients with exposure to other study drugs. The results from the unbalanced comparison between cohorts with large and small sample size may be misleading. Therefore, it is uncertain whether the low prevalence rate is due to the small sample size or the low NSF risk associated with certain GBCAs.

7.4.2.6 Short Follow-up Time from Exposure to End of Study

Although NSF can occur within days, it usually develops months after GBCA exposure. However, the incubation time can be as long as several years in some cases. In those studies with a follow-up period less than 1 year, patients may not have had time to develop clinically apparent NSF, which may have lead to an underestimation of NSF risk. For example, Janus[65] et al. only followed patients for four months after their exposure to gadolinium and found no case in their study. The same

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[65] Janus N, Launay-Vacher V, Karie S, et al. Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: results of the FINEST study. European Journal of Radiology. 2008, doi: 10.1016/j.ejrad.2008.11.021

problem was found with the Kallen[66] study where Optimark was used only five months before the end of the study period from August 2005 to 2006 while Omniscan was used in the other cohort from 2000 to July 2005. The study reported 10 and 3 cases of NSF in the Omniscan and Optimark cohorts, respectively. However, it is very likely that the cases were underestimated in the Optimark cohort because of the short follow-up time.

7.4.2.7 Under-Diagnoses of NSF

With the retrospective study design, many studies obtained the exposure and diagnosis information through medical charts. Therefore, those studies cannot definitively exclude other cases of NSF as patients were not monitored in a systematic manner. Even with prospective study design, mild and moderate cases are easily overlooked in the clinic if not specifically looked for. Because of the relatively recent identification of NSF, there may be undiagnosed or misdiagnosed NSF patients since the clinicians were not widely aware of this disease. For example, Prince et al. retrospectively identified seven NSF cases with review of pathology slides from those who were initially diagnosed as scleromyxedema or scleromyxedema-like disease associated renal failure[67]. Some studies cannot exclude that some NSF cases are still to be found among their patients due to short follow-up time and long incubation of NSF development. Also, we cannot exclude that some deceased patients suffered from undiagnosed NSF. Mortality risk seems to increase in patients with NSF as a study reported that the 24 months mortality was 48% and 20% in patients with and without NSF[68]. Therefore, it is very likely that the risk of NSF due to GBCA exposure was underestimated in the literature with those limitations discussed in this section.

7.4.2.8 Inappropriate Comparison

The Wiginton[69] study compared the prevalence of NSF between Omniscan and Magnevist cohorts. However, Magnevist was used in the study institution from late 1980 until September 2000 and Omniscan was used exclusively after September 2000. Since NSF was not described in the literature until 2000, the NSF cases in the Magnevist cohort may be largely under-diagnosed. Therefore, it is inappropriate to compare the estimated prevalence of NSF in the Omniscan and Magnevist cohorts directly in this study.

7.4.3 Off-Label Use

This review also identified several off-label uses of GBCAs in current medical practice. Dosages for these off-label procedures are not standardized, but often higher than the dose for MRI. Since there

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[66] Kallen AJ, Jhung MA, Cheng S, et al. Gadolinium-containing magnetic resonance imaging contrast and nephrogenic systemic fibrosis : a case-control study. American Journal of Kidney Disease. 2008; 51(6): 966-975

[67] Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology. 2008; 248(3): 807-816

[68] Todd DJ, Kagan A, Chibnik LB, et al. Cutaneous changes of nephrogenic systemic fibrosis-predictor of early mortality and association with gadolinium exposure. Arthritis & Rheumatism. 2007; 56(10): 3433-3441

[69] Wiginton CD, Kelly B, Oto A, et al. Gadolinium-based contrast exposure, nephrogenic systemic fibrosis, and gadolinium detection in tissue. AJR. 2008; 190: 1060-1068

is a dose-response relationship between GBCAs and NSF risk, more emphatic discouragement of off-label use and/or dose restriction may be warranted.

7.4.4 Acute dialysis and NSF prevention/Liver transplantation and risk of NSF

Although the American College of Radiology recommended beginning hemodialysis within 2 hours after GBCA administration, the benefits of prompt hemodialysis after gadolinium-enhanced imaging is not yet supported by the reviewed literature. This literature review identified very limited information on whether acute dialysis helps to prevent NSF in patients who are not on chronic dialysis. The same is true with data on whether recent liver transplantation is an independent risk factor of NSF. Further studies are needed to assess the risk of NSF among recent liver transplant patients and to study the effectiveness of immediate dialysis in preventing NSF for patients who are not on chronic dialysis.

7.5 SUMMARY OF LITERATURE REVIEW

This epidemiology literature review found that NSF risk differed by CKD severity. All NSF cases had either stage 4-5 CKD or acute renal failure. There is a dose-response relationship for GBCAs and the development of NSF. However, it is not clear whether the intensity of individual doses or the accumulation of doses, or both, determines risk.

There were more published studies that reported a higher prevalence of NSF among Omniscan users compared to Magnevist, Multihance, Prohance and Optimark. However, most of the studies had significant limitations that undermined the validity and generalizability of the study results. Therefore, based on this epidemiology review alone, no firm conclusions can be drawn at this time regarding the differential risk for NSF across GBCAs. Additional data or studies are needed to determine whether certain GBCAs are safer for use than others in patients with renal impairment. The ongoing post-marketing safety trials that were requested by the FDA to the sponsors may overcome some of the limitations discussed in this review and may provide the incidence data on these five GBCAs.

There is also insufficient evidence to determine whether recent liver transplantation is an independent risk factor of NSF or whether acute dialysis immediately after GBCA exposure is helpful in preventing NSF for patients who are not on chronic dialysis.

8 DISCUSSION

Symptomatic NSF is a rarely reported disease and its uncertain latency after administration of GBCAs renders its study problematic; no prospective, controlled studies have yet been performed to assess risk. Indeed, such studies may prove to be unfeasible or potentially unethical as accumulating data strongly supports significant renal dysfunction as a necessary precondition for NSF after GBCA exposure while, conversely, normal renal function is protective. Additional study feasibility concerns include the effects of prior regulatory actions and associated changes in clinical practice (presumably due to these regulatory actions) as well as publicity. This document reviews several lines of evidence, all of which have limitations, concerning differences in risk for the development of nephrogenic systemic fibrosis among five US-marketed gadolinium-bearing contrast agents. These lines of evidence are 1) physicochemical properties of the gadolinium-chelator complexes and the detection of gadolinium in tissues; 2) sales data; 3) postmarketing adverse event reports received through the MedWatch system and 4) literature regarding the association of NSF with administration of GBCAs.

Laboratory data provide support for the concept that the structure of the GBCAs may be important to deposition of free gadolinium in tissues; tissue deposition of gadolinium in animals is greater after administration of linear than macrocyclic agents. Macrocyclic gadolinium complexes are more stable than linear ones and release far less gadolinium, a known toxin, *in vitro*. There is *in vivo* evidence supporting the occurrence of transmetallation which promotes gadolinium dissociation from the chelator. However, other factors also may be important in the pathogenesis of NSF, such as dose intensity or numbers of doses, degree of renal failure, and other proposed factors such as tissue injury and high-dose erythropoietin.

The crude count analysis of all postmarketing reports received through the MedWatch system is not generally helpful for stratifying risk across GBCA products as the majority of reports are confounded by the naming of multiple suspect agents. Additionally, a differential risk analysis, while quantitatively problematic for stratifying risk due to batch reporting (because calculation of valid rates assumes independence of reporters), uncertainties in the quantities of GBCA given, and possibly by different definitions of NSF by manufacturers (for manufacturer-submitted reports), may nonetheless be qualitatively useful for informing an overall risk assessment . As such, it is notable that the highest number of single-agent reports are associated with Omniscan, Magnevist, and, proportionately, Optimark, and that there are no domestic reports with Prohance and one domestic report with Multihance.

Table 14 shows a comparison of the numbers of NSF single-agent cases since product launch with estimated volume (liters) sold of GBCAs from 2005-2007. While these numbers are imprecise for calculating quantitatively accurate risk ratios (due to limitations in the data that have been discussed previously in this review), they may, in the context of the totality of data considered in this review, be used to qualitatively inform overall risk. The time period for sales was selected as it covers most of the reported cases of NSF (a comparison using sales data from 2005 through June 2009 yields similar results). This comparison shows a similar magnitude of cases to volume of Magnevist, Omniscan, and Optimark sold, and a smaller magnitude for Multihance and Prohance, which were similar to each other.

Table 14. Volume of product sold and single-agent NSF cases

GBCA	Single-agent domestic NSF cases since launch of product	Total Volume sold, 2005-2007 (liters x1000)*
Magnevist	195	237
Omniscan	382	153
Multihance	1	19
Optimark	35	51
Prohance	0	23

*From Table 16, Estimated number of milliliters sold

Additional analysis of the cases with narrative mention of glomerular filtration rate showed the great majority of cases occurring in patients with severe renal dysfunction, consistent with the literature.

The disproportionality analysis of postmarketing reports is intended to compare the strength of association of a specific agent's exposure to the occurrence of NSF across GBCA products based on numbers of reports and cannot be used to infer absolute NSF risk for specific products. Notwithstanding the inherent limitations of AERS data, the disproportionality analysis supports the physicochemical data in that it suggests a greater likelihood of reported NSF after Omniscan and Optimark exposure compared with other GBCAs.

Published literature does not contain studies sufficiently designed and conducted to resolve the issue of differential risk for NSF among the GBCAs.

9 CONCLUSION

The different lines of evidence cited in this review all have limitations, some of which are substantial. These limitations are described in the review. However, based on the preponderance of the evidence in this review, it is OSE's judgment that GBCAs are associated with varying risk of NSF. Of the five GBCAs considered, the highest risk is associated with Omniscan, Magnevist, and Optimark while the lowest risk is associated with Prohance and Multihance.

While this document represents OSE's current thinking on the subject, we note that the field of NSF research is rapidly evolving; as such, additional information may become available that will merit consideration at the upcoming Advisory Committee meeting.

10 RECOMMENDATIONS

OSE believes that the magnitude of NSF risk does not compel removal of specific GBCAs from the US market. However, based on the accumulated evidence, much of which has become available to FDA since the Agency recommended class labeling, differential risk-based labeling for GBCAs is warranted. OSE will work with the Division of Medical Imaging and Hematology Products and manufacturers to develop labeling that is consistent with the levels of risk and the benefits of the GBCAs.

11 APPENDICES

11.1 APPENDIX 1

<u>Warning Regarding NSF in GBCA Labeling</u>

> Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with noncontrast enhanced MRI. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a gadolinium based contrast agent in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.
>
> Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a gadolinium-based contrast agent and the degree of renal function impairment at the time of exposure.
>
> Postmarketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following the sequential administrations of gadodiamide with gadobenate dimeglumine (Multihance®) or gadoteridol (Prohance®). The number of postmarketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific gadolinium-based contrast agent.
>
> The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency

who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006;17:2359). The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any readministration

11.2 APPENDIX 2

11.2.1 Appendix 2.1

Drug Sales Database Description

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. The data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

11.2.2 Appendix 2.2

Drug Use Database Description

Premier RxMarket Advisor™

Premier RxMarket Advisor™ is a hospital drug utilization and financial database. Information is available from over 590 acute care and pediatric facilities and includes approximately 38 million inpatient records. On an annual basis, this constituted roughly one out of every six inpatient discharges in the United States, based on an analysis published in 2003.[70]

The hospitals that contribute information to this database are a sample of both Premier and U.S. institutions. Data are collected from this sample of participating hospitals with characteristics based upon geographic location, bed size, population served, payors and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups.[71] Based upon these analyses, FDA believes that most estimates of national inpatient drug use based on Premier data appear to be reasonable.

11.3 APPENDIX 3

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[70] National Center of Health Statistics. Health United States, 2003.

[71] Staffa JA. Gutierrez B, Kornegay C, et al. Outcome-based evaluation of a method for obtaining U.S. national estimates of inpatient drug utilization. Pharmacoepidemiology Drug Safety 2003;12: S173

Sales and Amount of Products Sold

Table 15. Sales Data* in Total Number of Vials (Eaches) of GBCA Products by Setting, January 2005 to June 2009

	Year 2005		Year 2006		Year 2007		Year 2008		Jan 2009-Jun 2009	
	Eaches	Share	Eaches	Share	Eaches	Share	Eaches	Share	Eaches	Share
	N(000)	%	N(000)	%	N(000)	%	N(000)	%	N(000)	%
GBCA Products Total	8562.5	100.0%	8672.9	100.0%	8278.1	100.0%	7740.3	100.0%	3938.6	100.0%
Non-Federal Hospitals	5496.4	64.2%	5489.8	63.3%	5122.4	61.9%	5009.6	64.7%	2598.3	66.0%
Clinics	2773.1	32.4%	2883.5	33.2%	2865.9	34.6%	2463.5	31.8%	1199.6	30.5%
All Other Outlets	293.1	3.4%	299.6	3.5%	289.9	3.5%	267.4	3.5%	140.7	3.5%
Magnevist (gadopentetate)	4012.3	46.9	3630.1	41.9	3748.1	45.3	3892.8	50.3	1976.9	50.2
Non-Federal Hospitals	2488.3	62	2134.9	58.8	2288.7	61.1	2546.6	65.4	1332.3	67.4
Clinics	1352.8	33.7	1343.3	37	1306.9	34.9	1189.3	30.6	562.6	28.5
All Other Outlets	171.3	4.3	152	4.2	152.6	4	157	4	82	4.1
Omniscan (gadodiamide)	3022.9	35.3	3421.2	39.4	2352.6	28.4	1583.7	20.5	756.7	19.2
Non-Federal Hospitals	2209.6	73.1	2564.4	75	1720.4	73.1	1148.5	72.5	546.6	72.2
Clinics	751.1	24.8	779.6	22.8	586	24.9	406.8	25.7	196.4	25.9
All Other Outlets	62.2	2.1	77.2	2.2	46.2	2	28.4	1.8	13.8	1.9
MultiHance (gadobenic acid)	98.4	1.1	253.7	2.9	751.5	9.1	1021.4	13.2	577.3	14.7
Non-Federal Hospitals	66.5	67.6	181.5	71.5	513.2	68.3	664.9	65.1	371.1	64.3
Clinics	29.4	29.9	64	25.2	214.9	28.6	324.2	31.7	184.5	32
All Other Outlets	2.5	2.5	8.1	3.3	23.6	3.1	32.4	3.2	21.7	3.7
Optimark (gadoversetamide)	898.1	10.5	935.7	10.8	1005.1	12.1	810.2	10.5	397.5	10.1
Non-Federal Hospitals	455.7	50.7	406.4	43.4	387.5	38.6	408.1	50.4	212.8	53.5
Clinics	405.9	45.2	487.7	52.1	575.1	57.2	378	46.7	174.6	43.9
All Other Outlets	36.5	4.1	41.4	4.5	42.5	4.2	24.2	2.9	10.1	2.6
Prohance (gadoteridol)	530.8	6.2	432.2	5	420.8	5.1	432.3	5.6	230.2	5.8
Non-Federal Hospitals	276.4	52.1	202.6	46.9	212.6	50.5	241.6	55.9	135.5	58.9
Clinics	233.9	44.1	208.9	48.3	183	43.5	165.2	38.2	81.5	35.4
All Other Outlets	20.7	3.8	20.8	4.8	25.3	6	25.5	5.9	13.3	5.7

* Source: IMS Health, IMS National Sales Perspectives™, Year 2005-2009, extracted 8-09.

Note: The table shows percents of use by each setting for each product, not as a percent of overall sales of all products.

Table 16. Estimated number of milliliters sold* GBCA Products, January 2005 to June 2009

	Year 2005		Year 2006		Year 2007		Year 2008		Jan 2009-Jun 2009	
	mL	Share	mL	Share	mL	Share	mL	Share	mL	Share
	N(000)	%	N(000)	%	N(000)	%	N(000)	%	N(000)	%
GBCA Products Total	158,227	100.0%	166,054	100.0%	160,279	100.0%	150,820	100.0%	76,549	100.0%
Magnevist (gadopentetate)	78,179	49.4%	77,620	46.7%	81,371	50.8%	84,633	56.1%	42,925	56.1%
Omniscan (gadodiamide)	52,926	33.4%	59,727	36.0%	40,695	25.4%	27,350	18.1%	13,047	17.0%
MultiHance (gadobenic acid)	1,709	1.1%	4,481	2.7%	13,215	8.2%	17,458	11.6%	9,858	12.9%
Optimark (gadoversetamide)	16,432	10.4%	16,988	10.2%	17,839	11.1%	14,094	9.3%	6,894	9.0%
Prohance (gadoteridol)	8,980	5.7%	7,238	4.4%	7,159	4.5%	7,285	4.8%	3,825	5.0%

* Source: IMS Health, IMS National Sales Perspectives™, Year 2005-2009, extracted 8-09.

11.4 APPENDIX 4

Discharges and Unique Patients Associated with a Hospital Billing for a GBCA Product in the U.S., January 2005 to May 2009

Table 17. Discharges Associated with a Hospital Billing for a GBCA in the U.S., January 2005 to May 2009

	2005		2006		2007		2008		YTD 2009 (Jan - May)		Total (Jan 2005 - May 2009)	
	Discharge	Share	Discharge	Share	Discharge	Share	Discharge	Share	Discharge	Share	Discharge	Share
Product Name	N	%	N	%	N	%	N	%	N	%	N	%
Total	71,423	100.0%	121,890	100.0%	139,572	100.0%	143,119	100.0%	56,448	100.0%	532,452	100.0%
Magnevist	38,508	53.9%	46,649	38.3%	44,703	32.0%	45,794	32.0%	16,377	29.0%	192,031	36.1%
MultiHance	0	0.0%	13	0.0%	2,154	1.5%	7,135	5.0%	3,429	6.1%	12,731	2.4%
Optimark	1,207	1.7%	3,651	3.0%	4,239	3.0%	4,321	3.0%	2,144	3.8%	7,001	1.3%
Omniscan	6,115	8.6%	11,586	9.5%	8,226	5.9%	3,984	2.8%	2,112	3.7%	15,530	2.9%
Prohance	382	0.5%	164	0.1%	419	0.3%	3,892	2.7%	1,541	2.7%	31,452	5.9%
Gadolinium (Unspecified)	25,211	35.3%	59,827	49.1%	79,831	57.2%	77,993	54.5%	30,845	54.6%	273,707	51.4%

Premier Healthcare Informatics, RxMarket Advisor™, data extracted 8-09.

Table 18. Total Number of Unique patients Associated with a Hospital Billing for a GBCA Product in the U.S., January 2005 to May 2009

	2005		2006		2007		2008		YTD 2009 (Jan - May)		Total (Jan 2005 - May 2009)	
	Unique Patients	Share	Unique Patients	Share	Unique Patients	Share	Unique Patients	Share	Unique Patients	Share	Unique Patients	Share
Product Name	N	%	N	%	N	%	N	%	N	%	N	%
Total	67,837	100.0%	115,816	100.0%	132,481	100.0%	135,958	100.0%	54,694	100.0%	489,546	100.0%
Magnevist	36,509	53.8%	44,405	38.3%	42,369	32.0%	43,524	32.0%	15,823	28.9%	176,174	36.0%
MultiHance	0	0.0%	13	0.0%	2,079	1.6%	6,865	5.0%	3,329	6.1%	12,092	2.5%
Optimark	1,159	1.7%	3,441	3.0%	4,032	3.0%	4,102	3.0%	2,061	3.8%	14,342	2.9%
Omniscan	5,831	8.6%	11,046	9.5%	7,883	6.0%	3,797	2.8%	1,493	2.7%	29,224	6.0%
Prohance	373	0.5%	163	0.1%	409	0.3%	3,741	2.8%	2,078	3.8%	6,652	1.4%
Gadolinium (Unspecified)	23,965	35.3%	56,748	49.0%	75,709	57.1%	73,929	54.4%	29,910	54.7%	251,062	51.3%

Premier Healthcare Informatics, RxMarket Advisor™, data extracted 8-09.

11.5 APPENDIX 5

<u>Number of Hospitals Reporting GBCA by Specific Product in Premier's Database, January 2005 to May 2009</u>

Year	Number of Hospitals (N)
2005	101
2006	129
2007	150
2008	182
YTD to May 2009	142

Email Correspondence: Walsh, Allison (Allison_Walsh@PremierInc.com), 9/4/2009. Re: Premier question for GBCA

11.6 APPENDIX 6

<u>Narratives of Medwatch Reports of Association Between NSF and Gbca With GFR reported ≥30 ml/min/1.73 m^2</u>

<u>Omniscan</u>

AERS ISR#6237731 Mfr # OSCN-PR-0905S-0272 FDA receipt date: 6/11/09

The patient was a 55 year-old African-American female with diabetes mellitus, chronic renal failure due to diabetic nephropathy, diabetic neuropathy, secondary hyperparathyroidism, malignant hypertension, coronary artery disease, status post myocardial infarction x2, morbid obesity, congestive cardiac failure, status post cholecystectomy, and a surgical history of hernia repair and tube ligation. On [redacted] (b) (6), she presented to the Emergency with right-sided numbness and weakness and was admitted to hospital with a presumptive diagnosis of cerebrovascular accident, commenced a low-dose heparin protocol and sliding-scale insulin, underwent MRI/MRA of the head and neck with and without contrast, and the next day renal MRA with contrast. Both contrast procedures were done with 30ml Omniscan, a cumulative dose 60 ml within 24 hours. eGFR at the time of first administration was 33 mL/min/1.73m^2, at second administration 40 mL/min/m^2, and remained between 30 and 31 mL/min/1.73m^2 during hospitalization. She was later diagnosed as having a right thalamic infarction and stenosis of the posterior cerebral artery; renal arteries were suspicious of mild to moderate stenosis. After an unknown interval following Omniscan administration, she experienced a right-sided burning sensation, then, stiffening and hardening of the skin, particularly of the feet and extending to the legs. About 4 months after Omniscan exposure on [redacted] (b) (6) a skin biopsy was consistent with NSF diagnosis. The patient progressed to Stage IV chronic renal failure, and continued to experience NSF symptoms, although no specific treatment was being administered. She died on [redacted] (b) (6) due to complications of her underlying disease in which a contributory role of NSF was proposed.

Comment: The GE Healthcare response to FDA request for Information on GBCAs/NSF states that the extended MDRD formula results in an estimated GFR for this patient of less than 30ml/min/m^2 (27.9ml/min/m^2) on [redacted] (b) (6) and that 2 weeks after hospital discharge, the patient was in Stage IV chronic renal failure.

<u>Omniscan/Multihance</u>

AERS ISR#5332051 Mfr#US-BRACCO-BDI-009559 FDA receipt 12/5/08

A 49 year-old female with hepato-renal syndrome and liver transplant underwent two pre-transplant MRI studies with Omniscan in May and November 2004. On May 2004, with a GFR of 12 ml/min/m^2, she received 12 ml of Omniscan. On Nov 2, 2004, with a GFR of 24 ml/min/m^2 , she received 13 ml of Omniscan. After liver transplantation on [redacted] (b) (6), she underwent 2 additional MRI studies. In April and May 2005, with GFRs of 42 and 50 ml/min/m^2 respectively, she received 13 ml doses of Multihance for each study. Due to fibrotic skin changes, a skin biopsy was performed on July 7, 2005 showing unspecific fibrotic skin changes. A repeat skin biopsy on Oct 5, 2005 confirmed a diagnosis of NSF.

<u>Magnevist</u>

FDA ISR#5963610 MFR#US-BAYER-200833284NA FDA receipt 09/22/2008

A 59 year-old Caucasian male with history of uncontrolled hypertension and renal cysts received Magnevist (gadopentetate dimeglumine) (20 ml) during an MRI for right kidney cyst and to rule out stenosis on 31-Jul-2008. The patient also received Magnevist (20 ml) during an MRA (magnetic resonance angiography) of the kidney for the indication of right kidney cyst and to rule out renal artery stenosis on 04-Aug-2008. The diagnosis was complex cysts of the kidney and no evidence of renal stenosis. Relevant labs dated 07-May-2008: BUN 13 (7-18mg/dL), creatinine 0.9 (0.6-1.3mg/dL), eGFR 92.12 mL/min/1.73m^2. SGOT/AST 76 (15-37 U/L, SGPT/ALT 70 (30-65 U/L), glucose random 110 (65-105 mg/dL).On an unspecified date, the patient experienced possible nephrogenic systemic fibrosis. Patient denied a history of renal problems. Past drug therapy includes an unspecified gadolinium (contrast media) during MRI in 2004.

Comment: This case includes a diagnosis of "possible NSF" with no biopsy information. The GFR was determined 3 months before the MRI/MRAs and may not reflect the GFR at the time of administration of the GBCA.

FDA ISR#6292126 MFR#US-BAYER-200927617NA FDA receipt 7/27/09

A 63 year-old female with moderate renal impairment and an eGFR of 55 received Magnevist for an MRI. The patient subsequently developed nephrogenic systemic fibrosis proven by biopsy and low levels of gadolinium (6 ppm) were detected in skin lesions.

Comment: This report contains minimal information.

FDA ISR#6303018 Mfr#US-BAYER-200912213NA FDA receipt 2/5/09

A 93 year old male with history of chronic kidney disease received 20 ml Magnevist for a MRI of the brain and MRA of head and neck to evaluate mild cognitive difficulties on July 31, 2008. Patient also had a previous MRI in 2003 but it is unknown if contrast was administered. It was reported that the patient had an eGFR of 43 ml/min, however, it is unclear when the scan was performed to the proximity of the lab value. A few days after MRI, the patient experienced maculopapular rash diagnosed as eczematous dermatitis and was treated with steroids. In Sept 2008, the patient experienced tightening and hardening of skin on lower legs and thighs and tightening of skin on back and abdomen. He also had flexion contractures of elbows and knees. A skin biopsy was consistent with NSF and gadolinium was detected in the tissue. Patient was referred for treatment with Gleevec.

Comment: GFR at time of MRI/MRA is not documented.

Magnevist/Multihance

FDA ISR#5981598 Mfr#US-BRACCO-001781 FDA receipt date 12/5/08

A literature report: A 60-year-old white female patient presented to a rheumatology clinic with a chief complaint of increasing stiffness and skin thickening in her arms and legs of three months duration. Over the previous two years, the patient had had six MRI or magnetic resonance angiography examinations for peripheral vascular disease. Five of these exams included gadolinium-containing contrast media (total dose 105 ml of Multihance and 60 ml of Magnevist). Her medical history also included type 2 diabetes mellitus, coronary artery disease, hypertension, autoimmune hemolytic anemia, early stage breast cancer and chronic renal insufficiency. For the previous two years, the patient's serum creatinine levels had ranged between 159-177 mol/l (normal 62- 115 mol/l) and her estimated glomerular filtration rate had been around 30 ml/min/1.73 m (normal >60 ml/min/1.73 m). The patient had undergone right femoropopliteal bypass surgery for peripheral vascular disease nine years earlier. Several related surgeries on her lower extremities were done subsequently, the latest being a left above-knee amputation six months earlier. The patient's concomitant medications included hydralazine, isosorbide dinitrate, amlodipine, clonidine, aspirin, furosemide, gabapentin, and insulin. The patient's musculoskeletal symptoms started one month after her last MRI exam with contrast media (date and gadolinium contrast media unknown). She first experienced difficulty in walking because of stiffness and skin tightening, which started in her right lower leg, then gradually progressed to both of her thighs and upper extremities. She had not been treated with erythropoietin for anemia. She had not been exposed to chemicals such as vinyl chloride, benzene or toluene. She had no Raynaud's phenomenon, photosensitivity, mucosal ulcerations, skin rash or nodules. She denied cough, dyspnea, reflux symptoms or gastrointestinal bleeding. On physical examination, the patient was in no acute distress. Her blood pressure was 120/80 mmHg, pulse rate 70 beats/min, respiration rate 16 breaths/min, body temperature 97 °F, and oxygen saturation 97% in room air. The skin of her right leg, left leg stump, and upper arms was waxy, tight, and hyperpigmented. The skin of her face, hands, feet and trunk was normal. Her chest was clear to ausculation and percussion. A cardiovascular examination revealed a grade 1/6 systolic flow murmur at the left sternal border. The results of a joint exam were normal except for an 80° flexion contracture of her right knee. Distal and proximal muscle strength was normal bilaterally. Results of laboratory studies showed creatinine 153 µmol/l and eGFR of 28 ml/min/m^2. A diagnosis of nephrogenic systemic fibrosis (NSF) was made, and a trial of 400 mg of imatinib mesylate was initiated but was stopped after the first dose because of gastrointestinal intolerance. The patient subsequently received oral analgesics and extensive physical therapy. Three months after diagnosis, her skin thickness and the extent of limb stiffness had improved slightly. The patient receives ongoing symptomatic treatment, and is reassessed every 2 months.

Comment: Multiple gadolinium exposure with Multihance and Magnevist. It is unknown which gadolinium agent patient received last.

11.7 APPENDIX 7

Literature Selected for Detailed Review

Table 19. Literature summary of prospective cohort studies on the risk of NSF associated with GBCAs

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
Steen H[i]	2009	University of Heidelberg, Germany	136 pts	Pts on HD or PD before renal transplantation	Magnevist	0.28-0.34 ml/Kg	1			0.74% (1/136)	With a 16-mon follow-up, 1 pts developed NSF.
Schietinger BJ[ii]	Oct. 28, 2005-Aug. 22, 2006 then follow up for 23+/-3 mons	University of Virginia Health System	24	Pts age > 50 on HD with diabetes, or known cardiovascular disease	Omniscan (0/4) Magnevist (1/20)		2 (1 new case and 1 pre-existing case)		16 mons after Magnevist exposure, 25 and 33 mons after unknown Gd exposure	The estimated prevalence of NSF was 8.33% with 23 +/- 3 mons of follow-up.	1 new case of NSF was diagnosed in the Magnevist cohort, however, this pt had 2 prior exposure to unknown Gd. One subject with pre-existing NSF was enrolled.
Todd DJ[iii]	2007	6 outpt hemodialysis centers in Boston metropolitan area	54 exposed and 36 unexposed	Outpts on HD	Magnevist (16/54, 30%)		16(30%)	Adult pts on Hemodialysis		RR=10.7 (95% CI 1.5-76.9), OR=14.7 (95%CI 1.9-117.0) (16/54 pts exposed had NSF compared to 1/36 pts unexposed)	Mortality rate was 48% and 20% in pts with and without NSF in 24 mons follow up after NSF . Adjusted HR=2.9 (CI 1.4-5.9).
Panda S[iv]	2003-	Woodlands	2146	Pts on			6	5 cases were		0.28% (6/2146)	

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
	2006	medical Centre, Kolkata, India	pts	hemodialysis. 1545 (72%) were CKD 5, 578 (27%) acute renal failure, and 23 (1%) congenital polycystic kidney disease				CKD stage 5, one had acute tubular necrosis		pts postdialysis; 4.65%(2/43) in transplant recipients undergoing dialysis.	

Table 20. Literature summary of retrospective cohort studies on the risk of NSF associated with Gadolinium-based contrast agents (GBCAs)

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
Reilly RF[v]	2000-2007	Dallas Veterans Affairs hospital	141 pts with 198 Gd exposures	Pts on long-term hemodialysis. Pts with <14 days of follow-up after exposure were excluded. 1.4 +/- 0.8 Gd exposures per pt	Prohance (0/141)		0			0/198 exposures, 0/141 pts	Mean follow-up time 570+/- 474 days.
Chen WC[vi]	Jan. 2005 – Jul. 2007	A hospital in Taiwan	127 pts	Stage 5 CKD (GFR<15 ml/min) receiving HD and PD	Omniscan (1/81 pts)	0.1-0.2 mmol/Kg	1	24 yrs old on PD with systemic lupus erythematosus since age 15. Total cumulative dose of 50 ml in four procedures	9 mons after 1st exposure	Incidence: 1.23% (1/81) among 81 dialysis pts exposed; 0 case among 46 pts unexposed.	Mean follow-up period: 15.47+/-7.62 mons. Incidence of NSF in HD pts exposed was 0/67, in PD pts was 7.1% (1/14)
Othersen JB[vii]	2001-2006	Medical University of South Carolina	1441 pts	pts on chronic ambulatory dialysis (261exposed, 588 unexposed), 592 CKD 3 and 4 pts	Omniscan (191 pts once, 52 pts twice, 13 pts thrice, and 5 pts four times)	7.5-10 mmol	4		2-3 mons	OR=6.671 (95% CI 1.537-53.97) in pts with a single Gd exposure compared with non-exposed; OR=44.5 (2.362-	Prevalence rate was 1.1% (2/191pts) if pts exposed once, 2.9% (2/70) if exposed more than once, and 0% (0/588) if never exposed.

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
				exposed						2913) in pts with multiple exposure	No cases in 592 pts with stage 3 or 4 CKD
Deo A[viii]	Jan. 1, 2005-Jul. 1, 2006	Urban and suburban communities surround Bridgeport, CT	87 pts with 123 Gd studies	ESRD pts on hemodialysis or peritoneal dialysis	Omniscan	50, 125 ml for cases	2	ESRD on hemodialysis or peritoneal dialysis	< 2 mons	Incidence of NSF: 2.4% (3/123) per gadolinium exposure; 3.4% per pt exposed (3/87); 4.3 per 1000 pt-years (3/467 ESRD population exposed and unexposed) over 1.5 yrs).	2/3 cases had fatal courses. No case occurred in 380 pts unexposed.
					Magnevist	20 ml for the case	1				
Wertman R[ix]	Jan. 2000-Dec. 2006	University of North Carolina, Emory University, Wake Forest University, Thomas Jefferson University	82260 pts in Omniscan cohort	All pts exposed at tertiary care centers with renal transplant and dialysis services	Omniscan	Cumulative dose: 0.36 mmol/Kg,	32	Stage 4 or 5 CKD	15.4 wks (1-9.5)	The overall incidence of NSF associated with Omniscan was 0.039% (32/82260 pts). Incidence of NSF associated with Magevist was 0.003% (4/135347 pts).	The incidence of NSF were significantly higher in Omniscan users than that of Magnevist users, (p<0.001, OR=13.17, 95% CI 4.655-37.24).
			135347 pts in Magnevist cohort		Magnevist	0.43 mmol/Kg	4		14.5 wks (2.5-8.5)		
Prince MR[x]	Jan. 1, 1997 to June 30, 2007	New York-Presbyterian Hospital of Weill Medical College and	83121 pts	All pts exposed to Gds	Omniscan (O)(14/71441, 0.02%) Magnevist (Ma)(0/8669)	0.1 mmol/Kg, or higher dose	15	eGFR < 30 ml/min in all cases, 11 had acute renal failure or acute deterioration of chronic	18-102 days (mean 58 days)	Incidence with single high dose: O 0.18% (14/7844), Ma 0% (0/967), Mu 0.6%	Zero case in 74124 pts with the standard dose of GBCA; 15 (0.17%) of 8997 pts with high dose. Incidence

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
		Columbia medical Center			Prohance (P)(0/226) Multihance (Mu)(1/2785, 0.04%)			renal failure. Compared with pts without NSF, more pts with NSF had proinflammatory events, lower PH, younger age, lower eGFR, elevated serum phosphorus, and longer delay between Gd and hemodialysis		(1/166), P 0% (0/20). Incidence with GFR b/w 15 and 30: O 0.6% (2/2311), Ma (0/73), Mu (0/3), P (0/9); With GFR<15: O 10% (10/100), Ma (0/14), Mu (0/0), GFR<30 no acute renal failure: O 0.7% (4/552), Ma (0/94), Mu (0/9), P 0; Acute renal failure: O 10% (10/101), Ma (0/27), Mu 33% (1/3), P 0.	increased to 0.4% in pts in chronic hemodialysis receiving high dose of GBCA and to 8.8% in those whose eFGR < 15 ml/min but not undergoing hemodialysis; 19% (11/58) in pts with acute renal failure receiving high dose of Gd but did not had hemodialysis for at least 2 days after Gd. Zero case in 5725 pts with multiple 0.1 mmol/Kg doses of Gd compared with the incidence of 0.18% (9/5119) with a single high dose. Zero case in pts with an eGFR <15 ml/min received hemodialysis the same day of Gd administration.

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
Kane GC[xi]	Jan. 1998-July 2005	Mayo Clinic College of medicine, MN	95	Pts with SCr>=2 mg/dL that underwent percutaneous transluminal renal angioplasty	Prohance (48%) or Omniscan (52%)	20-116 ml	2	Both cases were hemodialysis-dependent with unspecified Gd exposure		2 cases were identified among 95 pts received Gd.	Note that some pts had additional Gd exposure that occurred around the same time.
Hope TA[xii]	Jan. 1, 2004-May 31, 2007	Northern California Kaiser Permanente	530 dialysis pts; 2862 CKD 4 and 5 pts not on dialysis	Pts on dialysis or had Cr>=1.8 mg/dl. Pts who died within 1 mon of exposure or left KP within 3 mons of exposure were excluded.	Magnevist	2808 (84%) pts had one MRI, and 16% had an average of 2.4 MRIs during study period	1 definite, 3 can't be ruled out	One case on hemodialysis for 13 yrs and had received 7 MRIs. Another one on chronic dialysis and 2 with CKD 4-5 not on dialysis.	355 days after last MRI	Prevalence of NSF 0.38% (2(1 definite and 1 possible case)/530) in dialysis pts, and 0.07% (2 possible cases/2862) in CKD 4 and 5 pts not on dialysis with an average follow-up of 1.78 years (SD: 0.93 yrs).	Only 10-15% of MRIs in this study used more than .0.1 mmol/Kg. Pts received an average of 1.21MRIs. This study may miss less significant NSF and underreport the true prevalence because this study relied on pts being referred to a specialists or having a clinician report the pts as having NSF.
Chrysochou C[xiii]	1999-2008	Salford Royal Hospital, UK	562 pts	Pts received renal Gd for renal MRAs with mean eGFR of 31	Omniscan (37 pts) Magnevist (521 pts)	0.1 and 0.2 mmol/kg	0			There was no case of NSF during median follow-up of 29 mons (3-102).	Note that pts with <11 wks follow-up were excluded.

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
				ml/min, range 5-133. (39.8% CKD3, 30.4% CKD4, and 14.4% CKD5, 5.3% on dialysis, 0.2% had renal transplant)	Vasovist (4 pts)						
Golding LP[xiv]	2002-2006	Moses H. Cone Hospital, Greensboro, NC	752 renal failure pts without infection and 80 renal failure pts with infection	Stage 4 CKD, acute renal failure, hemodialysis pts	Omniscan (7 cases), 1 case with no identifiable Gd exposure	0.10-0.31 mmol/Kg	8	7 cases were dialysis-dependent, 1 at stage 4 CKD (eGFR of 18) but not dialysis-dependent. 5 cases received Gd more than once	Median time from last Gd exposure to onset of NSF symptoms was 3 wks ranging from 2 days to 5 mons	Renal failure and infection: 6.3% (95% CI 2.7-13.8%), renal failure without infection 0.27% (0.07-0.96%), infection but no renal failure 0% (0-0.07%), neither infection nor renal failure 0% (0-0.006%)	
Shabana WM[xv]	Nov. 15, 1999-Dec. 31, 2006	University of Michigan Hospitals, MI	414 pts exposed, 699 pts unexposed	ESRD pts on long-term dialysis			12	This study also reported 29 NSF cases: 27 had chronic renal failure, 2 had acute renal failure. 19/25 (76%) were on dialysis.	Time b/w most recent Gd and symptom onset: < 1 mon in 8 pts, 1-2 mon in 7	2.9% (12/414 pts) developed NSF. Among those who had 1-2 exposures, 2.7% (9/330 pts); for those who had 3-4 exposures, 4.6%	No cases developed in 699 unexposed pts.

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
								Several of cases received standard doses of Gd	pts, 2-12 mons in 5 pts, and 53 mons in 1 pt.	(3/65 pts) developed NSF.	
Heinz-Peer G[xvi]	1997-2007	Medical University of Vienna, Austria	367 pts exposed, 146 pts unexposed	ESRD pts on HD or PD	Omniscan (O) (6 cases, 153 exams) Magnevist (Ma) (3 cases, 64 exams) Dotarem (D)(2 cases, 56 exams)	15, 20, 30, 75, 109, 90 ml	6	Age 49-77, 2 females and 4 males, 4 on HD and 2 on both HD and PD. 2 cases exposed only to O; 1 case exposed to Ma, then 2 doses of O; 1 case exposed to D and O; 1 case to O, Ma, and 3 doses of D; One case to 3 doses of O and 1 dose of Ma	Mean was 166 days (5-363 days)	Prevalence of NSF was 1.63% (95% CI 0.7-3.52%) in the exposed cohort, and 0% (0-2.56%) in the unexposed cohort. No case has been found in users of Gadovist(17 procedures), Prohance (15 procedures), Multihance (12 procedures), and Primovist (8 procedures).	Comparing the NSF prevalence rates of pts exposed to O at least once with pts who exposed to other Gd but never to O, no significant differences were obtained (p=0.222). This study also show a positive association b/w the cumulative dose of Gd and the risk of NSF.
Bridges MD[xvii]	Jan. 2002-Dec. 2005	Mayo Clinic Florida	61	Pts with moderate to end stage renal disease who had catheter angiography or CT with a high single	Omniscan	>=40 ml (median dose was 80 ml, range 40-200)	1	Long-term hemodialysis pt with end-stage diabetic vasculopathy waiting for renal-pancreatic transplantation	6 wks after 50ml Gd, 18 wks after 3 MRI procedure with an additional 100 ml	Prevalence of NSF was 1.6% (95% CI 0.04-8.8%) for all pts whose eGFR<60; 3.3% (0.08-17.2%) if eGFR<30; and 9.1% (0.23-	There was no case developed in 6 liver transplant pts during acute renal insufficiency.

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
				dose of Omniscan (at least 40 ml). Median eGFR was 30 (range 3-57).				, had MRSA infection immediately before Gd exposure.	Omniscan exposure in the 3 mons before.	41.3%) if eGFR<15 with at least 1 yr follow-up.	
Janus N[xviii]	July 1, 2005-July 1, 2006 then follow up for 4 mons after MRI	9 nephrology centers in France	232 exposed, 76 unexposed	18 years and older, reduced GFR (7.1% 60-90, 18.2% 30-60, 20.1% 15-30, 53.6% <15), and had at least one MRI	Dotarem (176 pts) Magnevist (46 pts) Omniscan (7 pts) Multihance (3 pts)		0			No NSF cases occurred within 4 mons after Gd exposure.	Limitation: only 4 mons of follow-up
Wiginton CD[xix]	1997-2007	University of Texas Medical Branch	63 pts with 104 MR exams	Dialysis patients	Omniscan (2/63)		2	Mean age of 47 yrs (range 14-87)		3.2% (2/63 pts)	18 patients underwent 23 MRI procedures with Magnevist and 0 NSF case developed; 63 pts underwent 104 MRI procedures with Omniscan and 2 cases of NSF were found.
			18 pts with 23 exams		Magnevist (0/18)		0			0% (0/18 pts)	
Rydahl C[xx]	Jan. 1, 2004-Mar. 21, 2006	Copenhagen University hospital,	190	CKD 1-5	Omniscan	24.0 mmol (lifetime	18	Stage 5 CKD	Mean follow up period: 29 mons (16-	Prevalence of NSF among pts with stage 5 CKD was 18/102	Prevalence among stage 5 CKD was 12% (95% CI 6-21)

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
		Herlev, Denmark				cumulated dose)			43 mons)	(18%, 95% CI 11-27%). No cases among 88 pats with stage 1-4 CKD (95% CI 0-4%).	with 1 gd exposure; 36% (18-59) with 2 exposure; 25% (1-80) with 3 exposure; 27% (13-46) with HD pts; 22% (7-48) with PD pts; 11% (5-23) without HD/PD.
Broome DR[xxi]	2000-2006	Loma Linda University Medical Center, CA	168 pts with 301 Gd based MRI and 258 non-Gd MRI	Dialysis pts	Omniscan	0.1-0.2 mmol/Kg	12	8 were dialysis-dependent chronic renal failure pts; 4 was acute renal failure pts. All cases had Omniscan at 0.2 mmol/Kg.	2-11 weeks	The prevalence of NSF was 4.0% of 301 Omniscan based procedures. OR was 22.3 (95% CI 1.3-378.9) (12 cases among 301 Gd based procedures vs. 0 case among 258 non-Gd based procedures)	Despite the fact that 10 cases were dialyzed within 2 days of Omniscan administration, this did not prevent the development of NSF.

Table 21. Literature summary of case-control studies on the risk of NSF associated with GBCAs

Study/Study Design	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
Kallen AJ[xxii] Matched case-control (1:3)	Dec. 2002-Aug. 2006	A hospital in St. Louis, Missouri	19 cases and 57 controls	Inpatients and outpatients on dialysis	Omniscan Optimark		19	Gd exposure couldn't be identified in one case.	14 cases had a median time from most recent MRI to date of NSF diagnosis was 123 days (range 5-242 days). Another 4 cases had Gd exposure between 16 and 68 mons before diagnosis.	Ten cases (53%) had received Omniscan and 3 cases (16%) had Optimark in the year prior to NSF diagnosis. Univariate OR for Omniscan in the past 1 yr was 9.83 (95% CI, 2.09-46.25); Optimark was 1.82 (95% CI, 1.82, 0.33-10.15).	Compared with those who didn't undergo MRI, ORs increased in a stepwise fashion for having 1 MRI (OR=4.41, 95% CI 1.01-19.24), 2 to 3 MRIs (OR=14.10, 95% CI 2.06-96.12), or 4 or more MRIs (OR=21.46, 95% CI 2.08-221.97)
Lauenstein TC[xxiii] Matched case-control (1:3)	Oct. 2003-Feb. 2007	Emory University Hospital, Atlanta, Georgia	312 pts exposed to Omniscan	Dialysis pts matched with cases on GBCA exposure, age (+/- 3 yrs), and gender	Omniscan		9	8 cases on hemodialysis, 1 case with kidney transplant not on dialysis	Average time interval between last Gd exposure and onset of NSF symptoms was 14 wks	Risk of NSF among dialysis pts exposed to Omniscan was 2.6% (8/312).	No significant differences in the average Gd dose for the last MRI or the mean total lifetime Gd doses.

Study/Study Design	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
									(range 2-42 wks).		
Collidge TA[xxiv] Case-control	Jan. 1, 2000-July 1, 2006	Two city teaching hospitals in west Scotland	1826 pts (421 pts exposed to 542 Gd exams)	Adult dialysis-dependent pts who underwent renal replacement therapy for stage 5 CKD (eGFR<15 ml/min)	Omniscan	Median dose: 30 ml,	13 cases/ 480 procedures	Mean age at start of renal replacement therapy was significantly lower for the NSF cases at 48.3 yrs (p=0.022). No difference was found in average dose of Omniscan per scan between cases and controls (median dose 0.20 vs. 0.21 mmol/Kg, p=0.83).	Median 76 days (range 2-2395 days)	Relative risk 4.124 (95% CI, 3.49-4.87) following Gd exposure. 3.1% (13/421) of dialysis-dependent pts who exposed to Gd developed NSF.	Cases received higher total dose of Omniscan (45 vs. 30 ml, p<0.001), and a higher median cumulative dose of Omniscan (0.39 vs. 0.23 mmol/Kg, p=0.008), and underwent more Gd imaging than Gd-exposed controls.
					Magnevist	15 ml	0/13				
					Multihance	15 ml	0/41				
					Gadovist	15 ml	0/6				
					Vasovist	10 ml	0/2				
Sadowski EA[xxv] Case-control	Oct. 2002-Nov. 2006	University of Wisconsin	131 pts (June 2005-July 2006)	Hospitalized pts with Renal insufficiency (eGFR <60) and a proinflammatory event	Omniscan (12), Both Multihance. and Omniscan (1)	0.10-0.31 mmol/Kg	13 (Oct. 2002-Nov. 2006), 6 (June 2005-July 2006)	NSF cases had significantly decreased eGFR (19.3 vs. 28.8, p=0.01), more Gd exposures (2.2 vs. 1.53, p=0.002), higher mean sCr level (4.9	Median time from last Gd exposure to onset of NSF was 11.5 days, all within 6 mons.	1-year incidence of NSF was 4.6% (6/131) among hospitalized pts with eGFR <60 and had an proinflammatory event	Two NSF cases had eGFR between 30 and 60 ml/min/1.73 m^2, but had acute renal insufficiency. Mortality rate was 31% among NSF cases (4/13).

Study/Study Design	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
								vs. 2.9 mg/dL, p=0.01), significantly younger (p=0.01), more proinflammatory events (2.0 vs. 1.5, p<0.001), and more MR examinations per pt than the control group.			
Cheng S[xxvi] Matched case-control (1:3)	Dec. 2002-Aug. 2006	A hospital in St. Louis, Missouri	19 cases and 57 controls	Inpatients and outpatient on chronic dialysis			28	Case pts had younger median age (50 vs. 58, p=0.04), were more likely to be on peritoneal dialysis (36% vs. 0%), and had a longer median time on dialysis (27 vs. 10 mons).		The prevalence was 4.6 cases per 100 peritoneal dialysis pts and 0.61 per 100 hemodialysis pts.	Gd exposure (OR=8.97, 1.28-63.01), history of DVT (p=0.02, OR=3.37, 0.60-18.85), hypothyroidism (p=0.01, OR=4.18, 0.66-26.57), dependent edema (p=0.001, OR=3.15, 0.67-14.77).
Marckmann P[xxvii] Matched Case-control.	2006	Herlev hospital, Denmark		Stage 5 CKD pts matched on age and gender	Omniscan		19	Stage 5 CKD. . Severe cases seem to develop primarily among pts in regular hemodialysis			Higher cumulative Omniscan dose among cases compared with controls (0.41 vs. 0.31 mmol/Kg, p=0.05) and

Study/Study Design	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
								at exposure.			among severe cases (major disabilities with need of aiding equipment) (n=9) compared with non-severe cases (without or with only minor disabilities) (0.49 vs. 0.33 mmol/Kg, p=0.02), high-dose epoietin, higher serum ionized calcium, phosphate levels increase the risk of NSF.
Marckmann P[xxviii] Case control	Aug. 2005-May 2006	Copenhagen University Hospital	370 exposed, 430-630 unexposed	ESRD pts	Omniscan	Mean dose of last MRI was 18.5 mmol (range 9-25) among cases. Cumulative dose from 11-63 mmol	13	Mean age a first sign of NSF was 50 yr (range 33-66), which is younger than the average ESRD pts (50 yr vs. 65 yr). 7 cases on hemodialysis, 1 on peritoneal dialysis, and 5 not on dialysis	25 days (range 2-75 days)	OR between 32.5 (95% CI 1.9-549.2) and 47.6 (95% CI 2.8-804.0) (13 cases among 370 exposed ESRD pts, 0 cases among 430-630 unexposed)	Omniscan use in ESRD pts was stopped from March 21, 2006. No new NSF cases after that date.

Study/Study Design	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
Cowper SE[xxix] Matched case-control (1:3)	May 1997-Nov. 2000	A hospital in California		Renal transplant patients			8				Case pts were more likely to have poor renal function post-transplantation then controls

Table 22. Literature summary of case series studies on the risk of NSF associated with GBCAs

Study	Study Time Period	Institution	Total cohort	Patient Population	Exposed GBCA	GBCA dose	Number of cases	Case Characteristics	Time from exposure to event	NSF Risk Assessment	Other Key Findings
Perez-Rodrigue z J[xxx]	2003-2008	Johns Hopkins hospital		Pts had Gd-enhanced MR examination s	Omniscan (20, 61%) Magnevist (7, 21%) Unknown (6, 18%) Gd exposure 1 yr before NSF diagnosis	0.15 mmol/K g 0.1 mmol/K g	33	Advanced renal failure (eGFR <15 ml/min/1.73 m^2). 26 pts had severe chronic ESRD and 7 had acute renal failure. 20 cases were on HD and 5 on PD. 18 cases had more than one Gd exposure within 1 year period	Mean interval: 29 days (range, 4-112 days)	2003-2006, the incidence rate of NSF was 36.5 cases per 100,000 procedure; 2007-2008, incidence rate was 4 cases per 100,000 procedures after renal function screening was implemented (p=0.001).	5 pts who received a liver transplant developed NSF within 3 mons after transplantation in the form of transient renal failure.
Grobner T[xxxi]	2006	General Hospital of Wiener Neustadt, Austria	9	ESRD pts on hemodialysi s	Omniscan		5	All NSF cases had metabolic acidosis, while unaffected pts showed normal PH value.	2-4 wks	56% (5/9 pts, 95% CI 26-81%)	Mean time on dialysis was longer in cases (36+/- 16.5 mons vs. 23.75 +/-12.5 mons)

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